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Original research

Investigation of the use of a sensor bracelet for the pre-symptomatic detection of changes in physiological parameters related to COVID-19: a prospective cohort study (COVI-GAPP)

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ABSTRACT

Objectives We investigated machine learning based identification of pre-symptomatic COVID-19 and detection of infection-related changes in physiology using a wearable device (the Ava bracelet).

Design Prospective cohort study.

Setting, participants and interventions Participants from a national cohort study in Liechtenstein were included in the current study. Nightly they wore the fertility bracelet that measured heart rate, respiratory rate, skin perfusion, heart rate variability and wrist-skin temperature. SARS-CoV-2 infection was diagnosed by molecular and/or serological assays.

Results A total of 1.5 million hours of physiological data were recorded from 1163 participants (mean age 44 +/- 5.5 years). COVID-19 was confirmed in 127 participants. Of these, 66 (52%) had worn their device from baseline to symptom onset and were included in the analysis with long short-term memory (LSTM) based recurrent neural networks (RNN). Multi-level modelling revealed significantly different values of physiological parameters in the pre- versus the post-symptomatic phase. The developed RNN algorithm had a recall of 0.73 in the training set and 0.68 in the testing set when detecting COVID-19 up to two days prior to symptom onset.

Conclusion Our proposed RNN algorithm identified 68% of COVID-19 positive participants two days prior to symptom onset. Wearable sensor technology can therefore enable COVID-19' detection during the pre-symptomatic period.

Trial registration ISRCTN - ISRCTN51255782: Can the Ava fertility tracker device detect early signs of COVID-19?

Strengths and limitations of this study

- Large sample size from a well-characterized and healthy national cohort.
- Wearable device technology combined with machine learning to monitor health parameters related to early detection of COVID-19 infections.
- Solely data from laboratory confirmed COVID-19 infections were used.
- Data from one single study centre may limit the generalizability of our findings.
- Small subsample of COVID-19 positive cases with sufficient high-quality data.

INTRODUCTION

One of the primary ways of controlling the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has involved the identification, tracing and isolation programs implemented by multiple countries globally [1]. In the current environment of variant SARS-CoV-2 strains, vaccine rollouts and searches for alternatives to quarantine, reverse transcription polymerase chain reaction (RT-PCR) and serological testing, surveys, temperature measurements, and symptom checks (e.g., fever) are used to identify patients with COVID-19 [2]. However, these methods are usually unable to identify pre-symptomatic or asymptomatic individuals.

Recent studies highlighted the need to identify potential cases prior to symptom onset to prevent virus transmission [2,3]. Commonly reported COVID-19 symptoms include fever, cough, chest tightness or difficulty breathing, fatigue, dyspnoea, myalgia, sputum production, headache, and gastrointestinal symptoms [4,5]. While molecular tests continue to be used to confirm infections, the logistics and costs of repeat or continuous testing across populations are prohibitive [6]. Recently, scientists have called for further research investigating whether wearable medical devices such as the Ava Fertility Tracker and direct-to-consumer products such as Fitbit [7], smartwatches [8] and other activity trackers [9] could be used for such surveillance [10] These devices can continuously monitor baseline temperature, heart rate, sleep duration, and/or activity levels, and subtle changes in these parameters could be used to indicate a potential infection.

Here, we aimed to assess the use of an existing, regulated wearable medical device (Ava Fertility Tracker) to evaluate COVID-19-related changes in various physiological parameters across four infection-related periods: incubation, pre-symptomatic, symptomatic, and recovery period. To our knowledge, this is the first prospective study of its kind that measures physiological changes in heart rate (HR), respiratory rate (RR), heart rate variability (HRV), wrist-skin temperature (WST), and skin perfusion to develop an algorithm to detect a pre-symptomatic COVID-19 infection.

MATERIALS AND METHODS

Study Design and Participants

All participants in the ongoing observational population-based prospective cohort study GAPP (Genetic and Phenotypic Determinants of Blood Pressure and Other Cardiovascular Risk Factors; *n* = 2170) in the Principality of Liechtenstein were invited to participate in the current study (COVI-GAPP) [11]. Since its inception in 2010, the GAPP study aims to better understand the development of cardiovascular risk factors in the general population (i.e., healthy adults aged 25 to 41 years) [12]. The only exclusion criterion with regard to participation in the COVI-GAPP study was not providing written informed consent. The first COVI-GAPP participants were enrolled in April 2020, and data used for this interim analysis were collected through March 2021 (*n* = 1163). The local ethics committee approved the study protocol, and written informed consent was obtained from each participant (BASEC 2020-00786).

Bracelet, App, and Participant Compliance

The Ava Fertility Tracker (version 2.0; Ava AG, Zurich, Switzerland) is an FDA-cleared and CE-certified fertility aid bracelet that complies with international regulatory requirements and applicable standards [13,14]. The wrist-worn tracker consists of three sensors that measure five physiological parameters simultaneously: HR, RR, HRV, WST, and skin perfusion (Figure S1). Although the bracelet measures multiple forms of HRV, we chose to focus on two time- and one frequency-dependent measurements: standard deviation of the normal-to normal interval (SDNN); root mean square of successive differences (RMSSD); and HRV ratio, respectively (see Supplementary Materials for more details of HRV measurements and rationale). Besides the physiological parameters of interest, the Ava device also measures sleep quantity (duration) and sleep quality via a built-in accelerometer. Prior studies have demonstrated how data from the device can inform a machine learning algorithm that detects ovulating women's most fertile days in real time with 90% accuracy [15]. Worn only while asleep, the bracelet saves data every 10 s and requires at least four hours of relatively uninterrupted sleep. The participant syncs their bracelet with a complementary smartphone app upon waking, transferring data from the device to Ava's backend system.

For COVI-GAPP's purposes, the app had a customized user functionality developed by the manufacturer. Participants could still see and monitor changes in physiological parameters in the app; however, they did not receive any messages or algorithm-driven interpretations of

their data (Figure 1A). Instead of answering fertility-related questions in-app, participants entered information related to behaviours that may have interfered with the physiological parameters of interest (e.g., alcohol, medication and drug intake, as such substances can alter central nervous system functioning; Figure 1B) [16]. The Daily Diary, as part of the custom app, enabled participants to record COVID-19-related symptoms, including chills, diarrhoea, dry cough, fatigue, fever, loss of smell, loss of taste, muscle or body aches and pains, nasal congestion or runny nose, shortness of breath or difficulty breathing, sore throat, vomiting (Figure 1C). To ensure the highest quality data possible, the study team reviewed a weekly compliance log; it indicated which participants had synced their bracelets with the app during the preceding week [17]. The study team followed-up with participants individually to mitigate operational challenges or log-in issues.

SARS-CoV-2 Antibody Testing and RT-PCR Testing

SARS-CoV-2 antibody tests were assessed at baseline (starting April 2020) and during follow-up (starting December 2020) by the medical laboratory Dr Risch Ostschweiz AG (Buchs SG, Switzerland) with an orthogonal test algorithm employing electrochemiluminescence (ECLIA) assays testing for pan-immunoglobulins directed against the N antigen and the receptor binding domain (RBD) of the SARS-CoV-2 spike protein, as described elsewhere [18]. Seroconversion was assumed if the first blood sample was negative for SARS-CoV-2 antibodies, but the second sample was positive.

If participants had any symptom during the study period, they were asked to go to the Liechtenstein national testing facility, which was open seven days per week. The centre allowed for higher testing frequencies than other European countries.[19] RT-PCR was performed either on a COBAS 6800 platform (Roche Diagnostics, Rotkreuz, Switzerland) or with the TaqPath assay on a QuantStudio 5 platform (Thermo Fisher Scientific, Allschwil, Switzerland), as described elsewhere [19–21]. Participants diagnosed with COVID-19 contacted the study team to discuss their symptoms and health status. Additionally, participants provided their date of symptom onset (SO) and overall symptom duration, enabling us to calculate a symptom end (SE) date.

Questionnaires

At the second antibody test, all participants were asked to complete a questionnaire providing personal information (age, sex), smoking status (current, past, never), blood group (A, B, AB,

O, unknown), number of children, living with household contacts who have tested positive for COVID-19, working with people who have tested positive for COVID-19, and vaccination status. We calculated body mass index (BMI) based on height and weights collected from the GAPP database.

Patient and Public Involvement (PPI)

Well characterized participants of the observational GAPP study were asked about their willingness to participate in this sub-study COVI-GAPP. Participants wore the bracelet overnight, answered questionnaires about symptoms and confounders and contributed blood for serological analyses. Periodically send video messages to all study participants as well as content and news about the study on the homepage (covi-gapp.li) ensured public and patient involvement. Any specific questions or concerns were directly addressed to the study team.

Statistical Analysis

Primary objective was to determine if different physiological parameters deviate from baseline during COVID-19 infection. Secondary, this information was used to develop a model predicting COVID-19 infection before symptom onset. To evaluate whether HR, RR, HRV, WST, and skin perfusion deviated from baseline measurements during the four infection-related periods, we categorized the daily parameter measurements as occurring at baseline if the day (d) was more than 10 days prior to symptom onset (SO; i.e., d > SO-10), the incubation period as SO-10 ≤ d < SO-2, and the pre-symptomatic period as SO-2 ≤ d < SO. Because participants' reported symptom durations varied, the measurements were categorized into the symptomatic infection category if SO ≤ d ≤ SE. Finally, parameters collected after symptom end (SE) were classified as being in the recovery period (i.e., d > SE).

Development of a Machine Learning Algorithm for Detecting Pre-Symptomatic COVID-19 Infection

We chose a recurrent neural network (RNN) with long short-term memory (LSTM) cells for the binary classification of an individual as healthy or infected (positive for COVID-19) on a given day. LSTM networks had proven highly accurate recognition of time series patterns and events across large datasets [22]. Its internal structure can memorize states and easily fetch or activate them even if they are created many epochs ago. The LSTM network we implemented

consisted of two hidden layers with 16 and 64 cells (Figure 2). Its output activation was a sigmoid function, while the recurrent activation was a hyperbolic tangent (tanh) function. The output was limited to the range between 0 and 1 to ensure that the model yields an overall probability of infection on a given day. Whenever this probability exceeded 0.5, a potential COVID-19 infection was indicated.

1. Data processing and multi-level model specification

We performed all data processing and analysis using R (v3.6.1) and Python (v3.6). After initial pre-processing of the data to remove potential artifacts and consistent with best practices [23] (see Supplementary Materials for detailed description), we ran a series of multi-level models with random intercepts and slopes to determine the differences in physiological parameters during the infection-related periods compared to baseline. Given our continuous criterion, we modelled our outcomes of interest using residual maximum likelihood estimation (REML) and Satterthwaite degrees of freedom. Four binary variables were created, indicating to which infection period a given measurement belonged (1 = belonging to that period, 0 = not belonging to that period). The reference baseline period measurements were encoded as 0 across all four binary variables. Reported results included the unstandardized regression coefficients for each effect. When multiple models were possible for the same parameter, we chose the model using the percentile of data (stable maxima) with the best fit (see Supplementary Materials). To ensure a family-wise alpha level less than or equal to 0.05, we implemented Bonferroni correction for the seven analysed parameters (corrected alpha level of $p = 0.007$) and adjusted how we defined marginal significance accordingly (i.e., $0.007 \leq p \leq 0.05$).

2. Data preparation and feature extraction for algorithm development

Because the Ava bracelet records over a million data points per use, we first identified the features most predictive of COVID-19. We normalized the night-time WST, RR and HR values to prime our model to detect deviations from baseline measurements and ensure greater stability in the measurements (e.g., to minimize inter-participant variability). Next, we compared the raw features' predictive performance before engineering novel, composite features. We conducted principal component analysis decomposition to test the correlation between the day of SO and other binary labelled features (e.g., alcohol consumption). We also

examined the correlation between WST and other physiological parameters to determine potential autocorrelation prior to model specification.

3. Training process

To limit our analysis to symptomatic COVID-19 cases, participants had to have reported a date of SO and recorded at least 28 days of bracelet data prior to that date; the full four weeks of data were required to ensure accurate baseline readings and enable the algorithm to account for cyclical variations in parameters attributable to monthly hormonal changes. Thus, each individual included in the analysis had at least 29 days of consecutive data recorded by the bracelet. We partitioned the data into 8-day sequences, enabling the algorithm to compare physiological parameters across 8-day windows. This meant that each user had more negative (class 0; "healthy" days) sequences in the distribution (e.g., [26, 19], [25, 18] [11, 3]) than positive sequences (class 1; "infected" days [e.g., SO-10 to SO-2] as shown in Figure 3). We selected a binary cross-entropy loss function for the RNN with a stochastic gradient descent (SGD) optimizer. Due to the sample size, we set the learning rate to 0.007 and 2000 epochs while also enabling an early stopping mechanism to prevent model overfitting. We trained our RNN 10 times, randomly splitting our sample into a training set (70% of participants) and test set (30% of participants) for each instance. We report the metrics of the best performing RNN model that was selected according to the following recall equation:

$$overall\_recall = ((recall\_class\_1\_train + recal\_class\_0\_train) * 0.7 + (recall\_class1\_test + recall\_class\_0\_test) * 0.3)/2$$

Finally, due to the number of COVID-19 cases compared to healthy days in our dataset, we up-sampled instances of class 1 via duplication such that it was represented in our training set 1.15 times more than a given negative sequence (i.e., class 0). Thus, the SGD optimizer treated the two classes as roughly equal and no longer overweighted the importance of the parameters predicting a healthy 8-day period. By training this LSTM model, we sought to leverage deep learning to predict the pre-symptomatic onset of COVID-19.

Role of the Funding Source

None of the funders of the study played a role in the study design, data collection, data analysis, data interpretation, writing of the report or decision to submit the paper.

RESULTS

Participants

A total of 1163 participants (mean age = 44.1 years, standard deviation [SD] = 5.6; 667 [57%] females) enrolled in the COVI-GAPP study (Figure 4). 127 participants (10.9%; 95% confidence interval, CI [9.3,12.8]) contracted COVID-19 during the study period. From these, 11 participants were hospitalised and three asymptomatic infected. As seen in Table 1, there were no differences in the sex ratio, age, BMI, or smoking status between individuals who did or did not test positive for COVID-19 during follow-up (all p values ≥ 0.30). A significantly higher proportion of participants who contracted COVID-19 reported household contacts (n = 58 of 1036 seronegative participants vs. 53 of 127 seropositive participants; $p < 0.001$) and/or work colleagues who also had COVID-19 (n = 230 of 1036 seronegative participants vs. 49 of 127 seropositive participants; $p < 0.001$). On average, COVI-GAPP participants wore the Ava bracelet for 1370.8 h over the course of the study (SD = 802.7), for a total of 1,453,006 h. Of the 127 participants who tested positive for COVID-19 via either PCR or antibody tests, only 66 users had worn their bracelet at least 29 days prior to SO what enabled enough data quality. From these 66 participants, COVID-19 infection was confirmed by RT-PCR test and SARS-CoV-2 antibody test (n = 48) or only by antibody test (n = 18).

1. Participants with confirmed COVID-19

Table 2 shows the clinical characteristics of COVID-19 positive participants, stratified according to their compliance wearing the bracelet prior to SO. A series of 26 analyses of variance (ANOVAs) and chi-square tests with Bonferroni correction revealed only BMI varied significantly between the two groups; non-compliant participants had a higher mean BMI (25.8 kg/m^2, SD = 4.0) than their compliant peers (23.8 kg/m^2, SD = 3.7; $F(1, 116) = 10.39$, p = 0.002).

2. Compliant participants with confirmed COVID-19

Among the 66 compliant participants who had COVID-19, 13,248 nights of data were collected (mean duration = 200 nights, SD = 47; range 72–284 nights) for a total of 124,079 h (mean hours per participant = 1880, SD = 461.8). Compliant participants had a mean age of 42.9 years (SD = 5.6), and most had never smoked (*n* = 57; 86%). Their COVID-19 symptoms lasted for an average of 8.5 days (SD = 5.0; range 1–25 days). Table 2 documents the frequency of their self-reported symptoms.

Physiological Changes During the Clinical Course of COVID-19

Employing multi-level modelling, we observed significant changes in five (RR, HR, HRV, HRV ratio and WST) of the seven device-measured physiological parameters during the pre-symptomatic, symptomatic, and recovery periods of COVID-19 compared to baseline. Table 3 provides the unstandardized coefficient values for each statistical model. The complete courses of the different physiological parameters are shown in Figure 5. Additional information about the intraclass correlation coefficients, including the relative residual variance explained by participant grouping, can be found in S2.

1. Respiration rate

COVID-19 positive participants had a significantly higher RR during the symptomatic period than at baseline ($\beta_{intercept}$ = 15.1 breaths/min, standard error [s.e.] = 0.26; p <0.0001); controlling for intra-individual variance, nightly RR increased by 1.0 breaths/min (s.e. = 0.18; p <0.0001). There were no significant differences in RR detected between baseline and other periods (all p's ≥ 0.114).

2. Heart rate

At baseline, participants had a resting nightly HR of 55.4 beats per minute (bpm; s.e. = 0.83; p < 0.0001). During the incubation period, individuals' HR increased significantly by 0.87 bpm (s.e. = 0.29; p = 0.004). HR remained elevated in the pre-symptomatic period, expected to be 1.0 bpm higher than during baseline (s.e. = 0.36, p = 0.007). HR continued to increase following SO, beating 2.2 bpm faster than at baseline (s.e. = 0.48, p < 0.0001). Finally, even after SE, participants had a significantly elevated HR (+0.87 bpm higher than baseline; s.e. = 0.22, p = 0.0002).

3. Heart rate variability: standard deviation of the NN interval

Compared to a baseline SDNN of 59.6 ms (s.e. = 1.4, $p < 0.0001$), participants had marginally significantly decreased SDNN in the incubation ($\beta_{incubation}$ = −1.5 ms, s.e. = 0.59; $p = 0.0149$), pre-symptomatic ($\beta_{pre-symptomatic}$= −1.7 ms, s.e. = 64; $p = 0.0086$), and symptomatic ($\beta_{symptomatic}$ = −1.4 ms, s.e. = 0.73; $p = 0.0499$) periods. Following SE, SDNN returned to baseline levels ($\beta_{recovery}$ = −0.9ms, s.e. = 0.51; $p = 0.0787$).

4. Heart rate variability: root mean square of successive differences

Our analyses did not reveal any significant phase-based differences in RMSSD for COVID-19 positive participants during their infection (all p's ≥ 157) compared to baseline ($\beta_{intercept}$ = 43.7 ms, s.e. = 1.2; $p \leq 0.0001$).

5. Heart rate variability ratio

As with SDNN, multi-level analysis revealed a marginally significant decreases in HRV ratio during the incubation ($\beta_{incubation}$ = −0.01, s.e. = 0.01; $p = 0.0361$) and pre-symptomatic periods ($\beta_{pre-symptomatic}$ = −0.02, s.e. = −0.01; $p = 0.0165$) compared to baseline ($\beta_{intercept}$ = 0.50, s.e. = 0.02; $p < 0.0001$). No significant difference in HRV ratio emerged between baseline and either the symptomatic or recovery period (all p's ≥ 0.5474).

6. Wrist skin temperature

Over and above participant level variance, WST increased by 0.13 °C (s.e. = 0.04; $p = 0.001$), 0.18 °C (s.e. = 0.05; $p = 0.001$) and 0.3 °C (s.e. = 0.05; $p < 0.0001$) during the incubation, pre-symptomatic and symptomatic periods, respectively, compared to baseline ($\beta_{intercept}$ = 35.3 °C, s.e. = 0.06; $p < 0.0001$). WST remained elevated by 0.2 °C relative to baseline even during the recovery period (s.e. = 0.03; $p < 0.0001$).

7. Skin perfusion

No changes in skin perfusion were observed when comparing measurements during infection (all p's ≥ 339) with baseline values ($\beta_{intercept}$ = −0.01, s.e. = 0.0; $p < 0001$).

Model Specification and Algorithm Performance

The best performing RNN consisted of composite features derived from the maximum nightly WST and median nightly RR averaged across the preceding three nights window. The other parameters dropped out. Table 4 summarizes the model performance metrics across the training and test samples. In the test set, the algorithm was able to detect 68% of COVID-19 cases two days prior to SO.

DISCUSSION

Our main objective was to assess the use of existing medical-grade technology in the early detection of changes in physiological parameters related to COVID-19, facilitating the early isolation and testing of potentially affected individuals to limit the spread of the SARS-CoV-2 virus. Our RNN algorithm, trained and tested using a 70:30 split, identified 68% of COVID-19 cases up to two days before SO in 66 participants with an accurate false-positive rate and laboratory-confirmed cases of SARS-CoV-2. We therefore demonstrated that a wearable sensor bracelet implemented alongside a machine learning model has the potential to detect COVID-19 infections prior to SO.

Our research constitutes one of the first prospective cohort studies using wearable sensor technology to gather real-time continuous physiological data upon which a machine learning algorithm for COVID-19's pre-symptomatic detection was trained. Compared to previous studies evaluating the use of different wearable devices and machine learning to identify COVID-19 infections based on self-reported COVID-19 infections [7–9,24–28] only laboratory-confirmed SARS-CoV-2 infections were used in this study. Mishra et al. [8], for example, evaluated the use of resting HR data from 32 infected Fitbit users to detect COVID-19 cases in real time and identified 62.5% of the cases before SO. Similarly, Miller et al. [24] used RR, HR, and HRV data from 271 WHOOP strap wearers to identify 20% of the participants who developed COVID-19 before SO and 80% by day three after SO. Our RNN algorithm detected 68% of laboratory-confirmed cases before SO, with additional statistical analyses revealing significant changes in WST, HR and HRV across the disease trajectory. Furthermore, our

algorithm included more concurrent physiological parameters than previous studies, such as nightly WST, RR, and cardiac data [7,8,24,29]. Unlike studies that performed retrospective measurements, our system was able to detect infections before SO. Uniquely, our research repurposed a previously existing CE-marked medical device for a novel purpose, illustrating a relatively inexpensive technique to detect pre-symptomatic COVID-19.

Our findings therefore suggest a wearable-informed machine learning algorithm may serve as a promising tool for pre- or asymptomatic detection of COVID-19. Based on this interim analysis, a 20,000-person RCT is currently underway to test the RNN algorithm's real-time efficacy; participants see and can act on real-time machine learning driven alerts about their likelihood of having a COVID-19 infection, ahead of when they may report symptoms [30]. Initial results from this larger prospective randomized, single-blinded crossover trial are expected in December 2022.

Strengths of our study include its population-based design and recruitment from a well-defined, well-characterized healthy cohort. A small subsample of COVID-19 positive users with sufficient high-quality data (wearing the bracelet ≥ 28 days prior to SO), reliance on data from a single national centre and the lack of ethnic diversity may limit the generalizability of our findings. Additionally, we could not exclude imprecision or misclassification errors related to which symptoms were experienced, dates of SO, and/or SE. As a final limitation, our defined model was not validated on a novel sample; however, a follow-up study currently underway will address this concern [30].

Overall, the COVI-GAPP study shows that pre-symptomatic detection of COVID-19-related changes in physiological parameters with a sensor bracelet is feasible. We found significant changes in WST, HR, and HRV occurring in COVID-19 positive patients during the pre-symptomatic period compared to wearable-detected baseline measurements, over and above the effects of intrapersonal variability. A novel machine learning algorithm detected 68% of laboratory-confirmed SARS-CoV-2 infections two days before SO. Wearable sensor technology represents an easy-to-use, low-cost method for enabling individuals to track their health and well-being during a pandemic. Our research shows how these devices, partnered with artificial intelligence, can push the boundaries on personalized medicine and detect illness prior to SO, potentially reducing virus transmission in communities. Future research should focus on how medical grade wearable sensor technology can aid in combatting the current pandemic by monitored sensor data.

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Institutional Review Board Statement: The study was approved by the Ethics Committee of Zurich, Switzerland (BASEC 2020-00786; date of approval: April 9th, 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Sharing Statement: Anonymized data that underlie the results reported in this article are available upon justified request to the corresponding author.

Conflicts of Interest: Lorenz Risch, and Martin Risch are key shareholders of the Dr Risch Medical Laboratory. David Conen has received consulting fees from Roche Diagnostics, outside of the current work. The other authors have no financial or personal conflicts of interest to declare.

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Table 1. Overall participant characteristics stratified according to whether they contracted COVID-19.

Variables	Total n=1163	COVID-19 n=127	No COVID-19 n=1036	Test Statistic	Significance (*p* value)
Sex ratio (F:M)	667:494	74:53	594:441	$\chi^2(4)=0{\cdot}40$	0·982
Mean age, years (SD)	44·08 (5·57)	43·66 (5·64)	44·14 (5·56)	F(1, 1071)=0·59	0·444
BMI, kg/m² (SD)	24·72 (3·97)	24·74 (4·00)	24·72 (3·97)	F(1, 1071)=0·02	0·90
Smoking status, *N* (never: current: past smoker)	654:110:102	93:10:12	561:100:90	$\chi^2(2)=2{\cdot}38$	0·304
***N* of household contacts with COVID-19**	111	53	58	$\chi^2(1)=127{\cdot}94$	<0·0001*
***N* of work colleagues with COVID-19**	279	49	230	$\chi^2(3)=27{\cdot}3$	<0·0001*

* *indicates p≤ 0·002, significant difference with Bonferroni correction*

Table 2. Clinical characteristics of participants who contracted COVID-19 stratified according to whether they did (compliant group) or did not (non-compliant group) wear the bracelet regularly.

Variables (n)	Compliant group (n=66)	Non-compliant group (n=61)	Test statistic	Significance (*p* value)
Sex ratio (F:M)	45:21	29:32	$\chi^2(1)=4{\cdot}74$	0·030
Mean age, years (SD)	42·88 (5·59)	44·54 (5·60)	F(1, 116)=2·85	0·094
BMI, kg/m² (SD)	23·75 (3·69)	25·81 (4·06)	F(1, 116)=10·39	0·002*
Hospitalization rate	3	7	$\chi^2(1)=0{\cdot}64$	0·425
Smoking status, *N* (never: current: past smoker)	57:4:5	36:6:7	$\chi^2(2)=3{\cdot}03$	0·22
N of household contacts with COVID-19	35	18	$\chi^2(1)=2{\cdot}39$	0·123
N of work colleagues with COVID-19	28	21	$\chi^2(1)=0$	1
COVID-19 symptoms:				
Fever	17	23	$\chi^2(1)=0{\cdot}89$	0·344
Chills	14	11	$\chi^2(1)=0{\cdot}62$	0·432
Cough	26	30	$\chi^2(1)=0{\cdot}25$	0·616
Runny nose	26	25	$\chi^2(1)=0{\cdot}01$	0·938
Difficulty breathing	11	10	$\chi^2(1)=0{\cdot}39$	0·530
Loss of the sense of smell	26	24	$\chi^2(1)=0{\cdot}37$	0·543
Loss of the sense of taste	20	22	$\chi^2(1)=0{\cdot}02$	0·896
Chest pressure	7	10	$\chi^2(1)=0{\cdot}22$	0·636
Sore throat	18	19	$\chi^2(1)=0{\cdot}00$	1
Muscle pain	27	32	$\chi^2(1)=0{\cdot}29$	0·593
Headache	44	29	$\chi^2(1)=7{\cdot}88$	0·005
Fatigue	27	38	$\chi^2(1)=2{\cdot}24$	0·135

Variables (n)	Compliant group (n=66)	Non-compliant group (n=61)	Test statistic	Significance (*p* value)
Malaise	19	25	$\chi^2(1)=0{\cdot}18$	0·670
Diarrhoea	13	13	$\chi^2(1)=0{\cdot}02$	0·896
Sickness	9	5	$\chi^2(1)=1{\cdot}29$	0·256
Vomiting	1	5	$\chi^2(1)=1{\cdot}89$	0·169
Hospitalization	3	7	$\chi^2(1)=0{\cdot}64$	0·425
Long-term effects of COVID-19 (≥10d)	5	15	$\chi^2(1)=5{\cdot}69$	0·017
Mean symptom duration	8·54 (5·10)	10·16 (10·98)	F(1, 116)=1·31	0·254

** indicates p≤ 0·002, significant difference with Bonferroni correction*

Table 3. Multi-level linear mixed models reveal the relationship between COVID-19 phases and physiological parameters.

Predictors		Wrist skin temperature	Heart rate	Heart rate variability (SDNN[1])	Heart rate variability (RMSSD[2])	Heart rate variability ratio	Respiratory rate	Skin perfusion
Intercept		35·32† (0.06)	55·43† (0.83)	59·64† (1.43)	43·71† (1.16)	0·50† (0.02)	15·10† (0.26)	-0·01† (0·00)
COVID-19 phase								
	Baseline	**Reference group**	**Reference group**	**Reference group**	**Reference group**	**Reference group**	**Reference group**	**Reference group**
	Incubation	0·13† (0·04)	0·87† (0·29)	-1·48* (0·59)	-0·37 (0·48)	-0·01* (0·01)	0·02 (0·06)	0·00 (0·00)
	Pre-Symptomatic	0·18† (0·05)	1·00† (0·36)	-1·70* (0·64)	-0·75 (0·53)	-0·02* (0·01)	0·14 (0·12)	0·00 (0·00)
	Symptomatic	0·30† (0·05)	2·15† (0·48)	−1·45* (0·73)	0·12 (0·51)	0·00 (0·01)	1·00† (0·18)	0·00 (0·00)
	Recovery	0·20† (0·03)	0·87† (0·22)	-0·92 (0·51)	0·04 (0·44)	0·00 (0·01)	0·10 (0·06)	0·00 (0·00)

Unstandardized β -coefficient values reported, with standard errors in brackets.

*Note: *, † refer to p< 0·05, 0·007, respectively, with Bonferroni correction.*

[1]*SDNN: standard deviation of the NN interval.*

[2]*RMSSD: root mean square of successive difference.*

Table 4. Performance metrics of the algorithm in the detection of COVID-19 two days prior to symptom onset. Class 1 represented an 8-day long training instance extracted from day 10 to day 2 before SO. Class 0 represented a training instance extracted from all other 8 days long consecutive measurements (e.g., SO-11 to SO-3). The training set consisted of 40 days measurements from 66 participants with 70:30 train-test split. Sensitivity is reflected in the recall of class 1, while specificity is determined by the recall of class 0.

Sample	Class	Precision	Recall	F-Score
Training Set	0	0.60	0.45	0.51
	1	0.60	0.73	0.66
Test Set	0	0.50	0.36	0.42
	1	0.54	0.68	0.60

Figure Legend

Figure 1.

COVI-GAPP participants (n=1163) wore a certified medical device at night while they slept, syncing it to a complementary smartphone application upon waking. The device and app were originally designed for fertility tracking in naturally menstruating women but adapted for the purposes of this study. Instead of real-time fertility indications, participants saw “Fertility Unknown” upon syncing (A). Additionally, the in-app Daily Diary asked participants about potential confounds (B) and COVID-19 symptoms (C) rather than fertility-related questions.

Figure 2.

Recurrent Neural Network (RNN) architecture for the detection of a pre-symptomatic case of COVID-19. The RNN consisted of two hidden layers and one output layer. The first hidden layer contained 16 and second layer contained 64 long short-term memory (LSTM) units. The LSTM output activation was a sigmoid function, while the recurrent activation on hidden layers was the ReLU (Rectified Linear Unit) function. The input of RNN was 8 consecutive values of physiological signal originating from 8 consecutive nights of data. The output was an indication about the potential COVID-19 infection.

Figure 3.

Class depiction based on the recurrent neural network (RNN). Here, class 0 represents healthy days and class 1 represents the pre-symptomatic phase of COVID-19 (SO-10 to SO-2). Vectors of marked classes represent training input for the RNN.

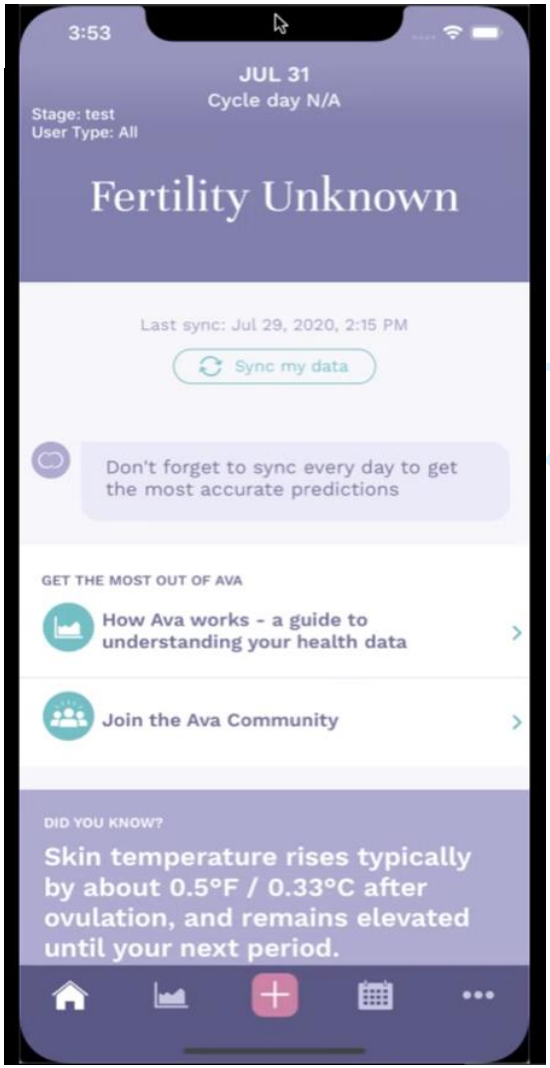
Figure 4.

Study flowchart. From 2170 GAPP participants, 1163 participants were enrolled in the COVI-GAPP study. 127 participants presented laboratory-confirmed COVID-19 disease and from these, a total of 66 positive tested participants had complete bracelet data available used for the algorithm development.

Figure 5.

The wearable device can detect changes in 5 physiological parameters across the clinical course of COVID-19. The values of each physiological parameter (with 95% CIs) collapsed across individuals (n=66) were normalized using baseline measurements and are shown centred around participant-reported symptom onset (SO).

A


3:53
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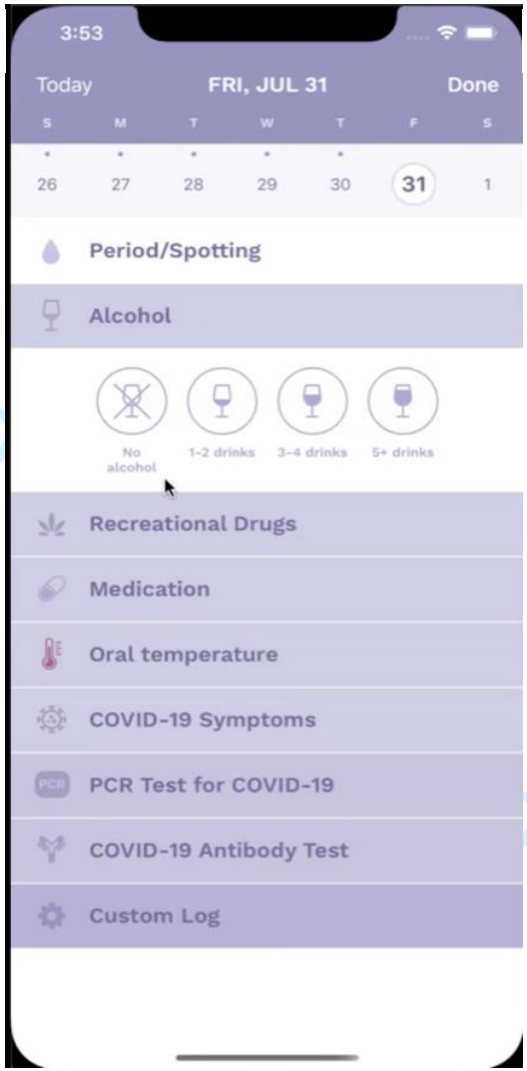
Don't forget to sync every day to get the most accurate predictions
GET THE MOST OUT OF AVA
How Ava works - a guide to understanding your health data
Join the Ava Community
DID YOU KNOW?
Skin temperature rises typically by about 0.5°F / 0.33°C after ovulation, and remains elevated until your next period.

B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Oral temperature
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PCR Test for COVID-19
COVID-19 Antibody Test
Custom Log

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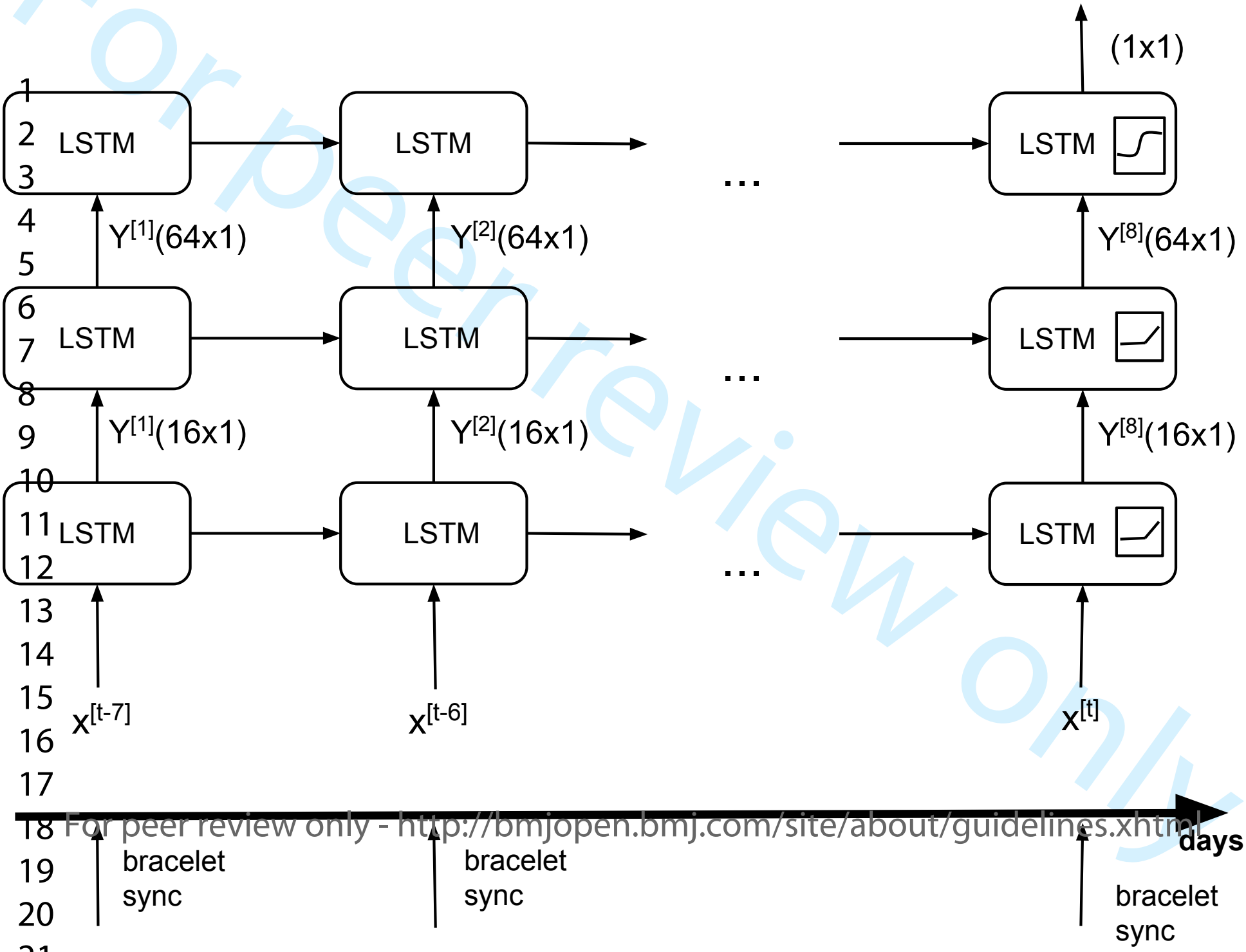
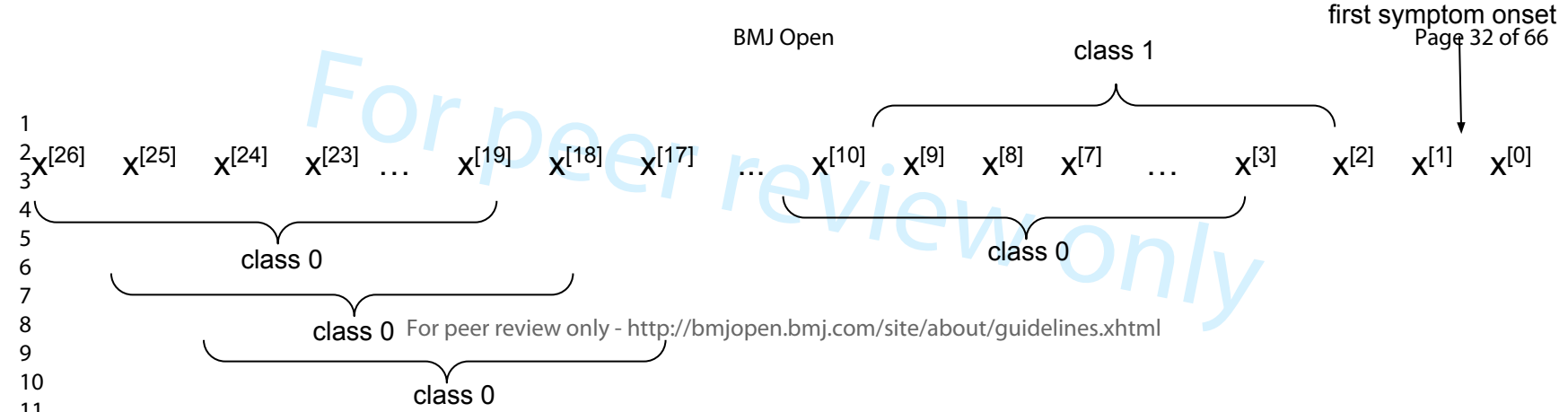
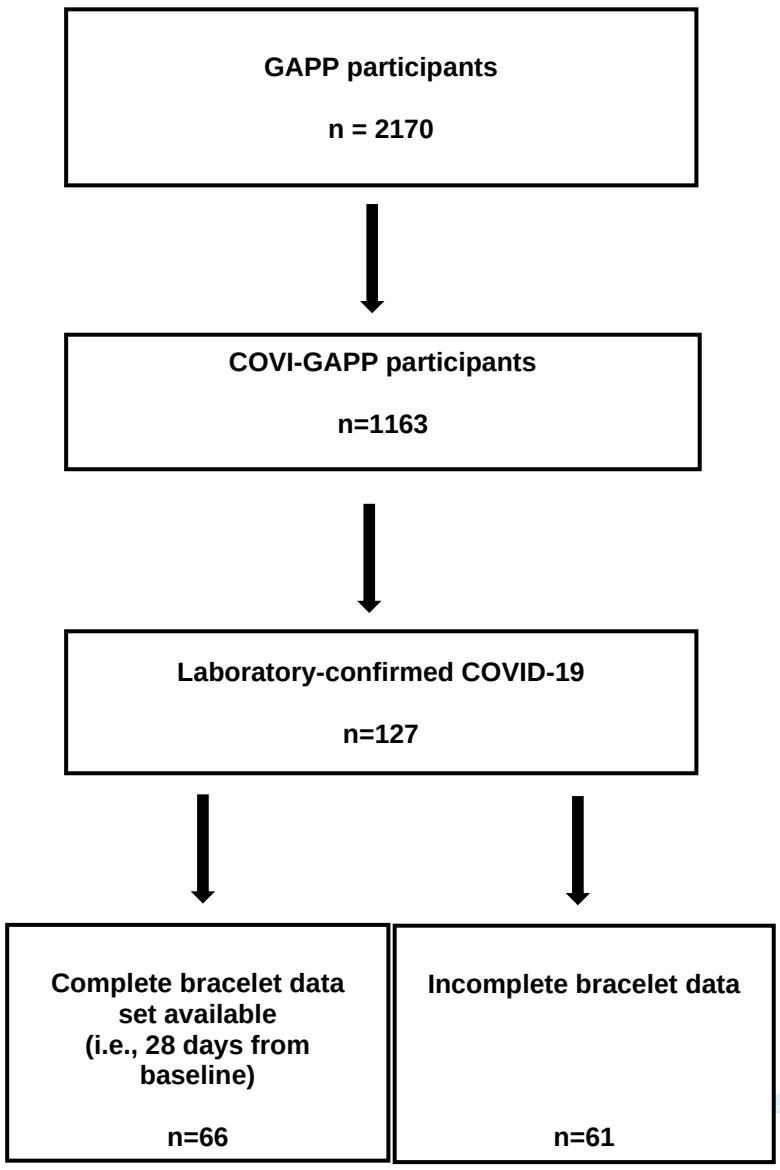
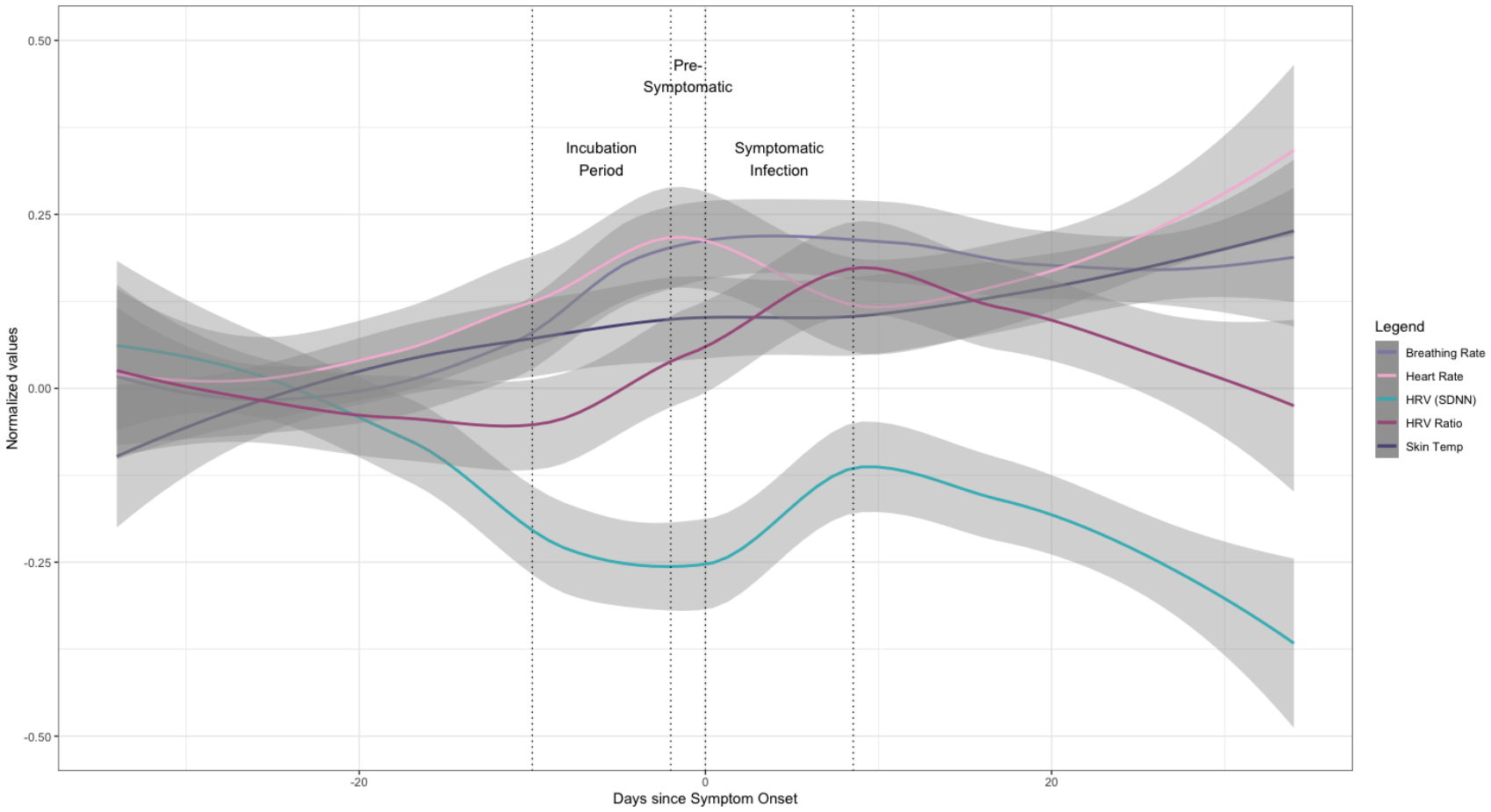
Chills
Diarrhea
Dry cough
Fatigue
Fever
Loss of smell
Loss of taste
Muscle or body aches
Nasal congestion or runny nose
Shortness of breath or difficulty breathing
Sore throat
Vomiting








Pre-
Symptomatic
Incubation
Period
Symptomatic
Infection
0.50
0.25
0.00
-0.25
-0.50
Normalized values
-20
0
20
Days since Symptom Onset
Legend
Breathing Rate
Heart Rate
HRV (SDNN)
HRV Ratio
Skin Temp

Appendix: Full list of the members of the COVID-19 remote early detection (COVID-RED) consortium.

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Supplementary Materials

Supplement to: "*Investigation of the use of a sensor bracelet for the pre-symptomatic detection of COVID-19: a national cohort study (COVI-GAPP)*".

Supplementary Material and Methods

Our primary aim was to understand how the coronavirus disease 2019 (COVID-19) affects physiological parameters measured by a wearable device and, subsequently, whether these parameter changes could help in detecting a pre-symptomatic infection. In particular, we investigated how heart rate (HR), respiratory rate (RR), heart rate variability (HRV), wrist-skin temperature (WST), and skin perfusion deviated from baseline measurements during four infection-related periods: the incubation period, the pre-symptomatic period, symptomatic infection period, and the recovery period. We categorized daily parameter measurements as occurring in the baseline period if the day (d) was more than 10 days prior to symptom onset (SO; i.e., d>SO-10). Relatedly, we defined the incubation period as SO-10≤d<SO-2 and the pre-symptomatic period as SO-2≤d<SO. Because participants' reported symptom duration varied, measurements fell into the symptomatic infection category if SO≤d≤SE. Finally, parameters collected after symptom end (SE) were classified as in the recovery period (i.e., d>SE).

The Wearable Device and Physiological Parameter Specification

The Ava Fertility Tracker (version 2·0; Ava AG, Switzerland) is an United States Food and Drug Administration (FDA) cleared and conformité européenne (CE) certified fertility aid bracelet that complies with international regulatory requirements and applicable standards.[1,2] The wrist-worn tracker consists of three sensors: a temperature sensor; an accelerometer; and a photoplethysmograph (PPG).[3] The bracelet saves data every 10 seconds and requires at least four hours of relatively uninterrupted sleep to record enough data for pre-processing and analysis. Upon waking, the user taps a button in the complementary smartphone app to initiate the previous night's raw data transfer from the bracelet to the system's backend database via Bluetooth Low Energy (BLE). The data then undergoes pre-processing according to proprietary manufacturer algorithms to remove potential artifacts, detect the user's sleep stages, and identify nightly physiological parameters. In addition to the algorithm-derived fertility indication, the post-processing values for HR, WST, RR, sleep quantity, sleep quality, and HRV ratio are then sent back to the complementary app and displayed to the user. The device's sensors responsible for recording the raw data are described in detail below as well as show in Figure S1.

Built into the Ava bracelet's internal hardware, the accelerometer detects and records the wearer's movement in three-dimensional space. A proprietary machine learning algorithm ingests nightly movement data to determine sleep stages. In addition to reporting the user's duration of sleep in-app, it also assigns her a nightly sleep quality score consisting of the percentage of combined deep and Rapid Eye Movement (REM) sleep. Although other researchers have examined COVID-19's impact on sleep using wearable devices with mixed or inconclusive results[4–7], since sleep quality and quantity were not among our pre-defined primary objectives we did not analyse results from the accelerometer data.

A temperature sensor constitutes the Ava Fertility Tracker's second sensor and provided data for evaluating COVID-19 related changes in wrist skin temperature (WST). Despite the device reading temperature at a distal point compared to core body temperature, recent research has demonstrated the bracelet's ability to continuously measure temperature throughout the night results in more sensitive readings than oral point estimates and enables its machine learning algorithms to detect more ovulation-related changes in temperature.[8] These findings suggest the medical grade device's ability to sense fluctuations in WST related to an infection would similarly benefit from its repeated sampling over the course of sleep and may outperform an oral or forehead reading taken only once at point of care (POC). Limited evidence conducted early on during the COVID-19 pandemic attests to WST's potential superior usage in detecting infection-based fluctuations; WST for 528 patients read by a noncontact infrared thermometer proved more stable and less prone to environmental factors (e.g., walking or bicycling to POC) than tympanic and forehead measurements in some contexts. Thus, given prior research on the Ava bracelet's measurement accuracy compared to oral temperature and on WST's importance in triaging COVID-19 patients, we relied on the device's temperature sensor to provide nightly WST readings for analysing how temperature changes across a symptomatic SARS-CoV-2 infection.

A PPG comprises the Ava bracelet's final sensor. The PPG sensor employs a light emitting diode (LED) current to send infrared light through the user's skin to detect inter-beat intervals (IBIs). The light reflects off or is absorbed by the blood; how much light bounces back to the sensor can signal the wearer's current cardiac rhythms.[9] Based on the time cadence for variance in the reflected light, proprietary algorithms can determine the user's HR, RR,

perfusion and IBI; in turn, the IBI can inform calculations for various metrics of HRV. While HR consists of the number of heart beats per minute, HRV describes the fluctuation in time intervals between consecutive heartbeats.[10] It can vary in both frequency- and time-domains, resulting in more than 20 possible metrics for quantifying the heart's activity.[10] Since examining all HRV metrics would have proven practically and statistically infeasible, we focused on two time- and one frequency-domain measurements. The first time-domain measure of HRV, the standard deviation of the normal-to-normal interval (SDNN), quantifies sympathetic and parasympathetic nervous system activity in ms; it describes how much variability exists in the interval between normal sinus beats.[10] A lower SDNN corresponds to impaired cardiac health[10], with recent research offering conflicting evidence about SDNN's changes in COVID-19 patients. While some studies demonstrated an increase in SDNN among COVID-19 patients[11], others have found changes in SDNN dependent upon disease severity.[12] Regardless of the effect's direction, we expected an individual suffering from COVID-19 would exhibit deviations from their baseline SDNN during an active infection and included it in our analyses. A second time-domain measurement of HRV, the root mean square of successive differences (RMSSD), examines the variability between normal heartbeats. Increased RMSSD has previously been shown to be associated with severe infection, including septic shock and COVID-19.[11,13] Thus, we focused on RMSSD changes across the incubation, pre-symptomatic, symptomatic and recovery phases compared to participants' baseline measurements in our analysis. The final HRV parameter we examined, the HRV ratio, constitutes a frequency-domain measurement; it indicates the ratio of HR oscillations in the low-frequency (LF; 0·04-0·15 Hertz [Hz]) to those in the high-frequency (HF; 0·15-0·4 Hz) bands[10,14]. Patients with severe COVID-19 infection have exhibited a higher HRV ratio than mildly infected participants[12], leading us to examine this physiological parameter in our analyses.

Data Processing and Multi-level Model Specification

We performed all data processing and analysis using R (R Core Team, v3·6·1[15]) and Python (Python Software Foundation, v3·6[16]). In keeping with data cleaning practices described by the manufacturer in previous publications,[3] we excluded the first 90 and the last 30 minutes of data from each night a priori from our analysis; transitions from waking to sleeping and vice versa can result in greater variation in physiological parameters measured by the Ava bracelet, thereby leading to less stable readings. To further reduce artificial fluctuations in the data due to potential measurement error and consistent with best practices[17], each physiological parameter underwent locally estimated scatterplot smoothing (LOESS) prior to analysis.

Next, we ran a series of multi-level models with random intercepts and random slopes to determine differences in physiological parameters during the infection-related periods compared to baseline, accounting for the nesting of repeated measurements during an infection period and within an individual. Given our continuous criterion, we used the "lme" function with residual maximum likelihood estimation (REML) and Satterthwaite degrees of freedom in the open-source R packages "lme4"[18], "lmerTest"[19], and "optimx"[20] to model our outcomes of interest. Four dummy-coded variables were created, indicating to which infection period a given measurement belonged (1= Belonging to that Period, 0=Not belonging to that period). The reference baseline period measurements were encoded as 0 across all four dummy variables. Our reported results include the unstandardized regression coefficients for each effect. When multiple models were possible for the same parameter, we chose the model using the percentile of data (stable maxima) with the best fit; we determined best fit by comparing the two models using an analysis of variance (ANOVA) test and selecting the model with the significantly lower Akaike Information Criterion (AIC). In instances where the models were not significantly different from each other, we chose the model that included more data (e.g., the 99% percentile of data versus the 90th percentile).

In an effort to provide some context for the magnitude of our significant effects, we report the intraclass correlation coefficient (ICC) for each of the null models associated with changes in physiological parameters over the course of a COVID-19 infection. The ICC indicates how much variance in an outcome occurs due to between group differences[21–23]; in the context of the current study, the ICC presents a picture of how a given physiological parameter varies due to participant-level characteristics versus the within-subject course of a COVID-19 infection.

To ensure a family-wise alpha level less than or equal to ·05, we implemented a Bonferroni correction for the seven total parameters we analyzed and evaluated effect significance using this new level of p=·007. We adjusted how we defined marginal significance accordingly (i.e., ·007≤p≤·05). We used the Bonferroni-corrected significance level throughout the paper.

Supplementary Results

The ICCs and random effects variance estimates for each of the seven multi-level models can be found in Table S1. In brief, most physiological parameters had high levels of variance which could be attributed to between participant differences rather than within subject changes due to COVID-19 infection.

For most physiological parameters, observed variance in the outcome resulted largely from a participant's own stability in readings over time. All cardiac parameters showed similar ICCs, ranging from 0·71 (RMSSD) to 0·77 (SDNN); this means that, depending on the parameter, 71-77% of the variance in outcome was due to between participant differences. Regardless of infection phase, a given participant's nightly cardiac measurements were more similar to one another than random chance. RR showed an even higher ICC; 88% of all observed variance in RR was attributable to between participant differences. A maximum of 22% of variance could be due to within participant changes. The multi-level model testing the effect of infection phase on nightly RR reveals only a significant difference between the symptomatic period and baseline (see Table 3); all other phases do not differ significantly from baseline, illustrating the lack of overall variability due to a COVID-19 infection and emphasizing RR's stability over time within an individual participant.

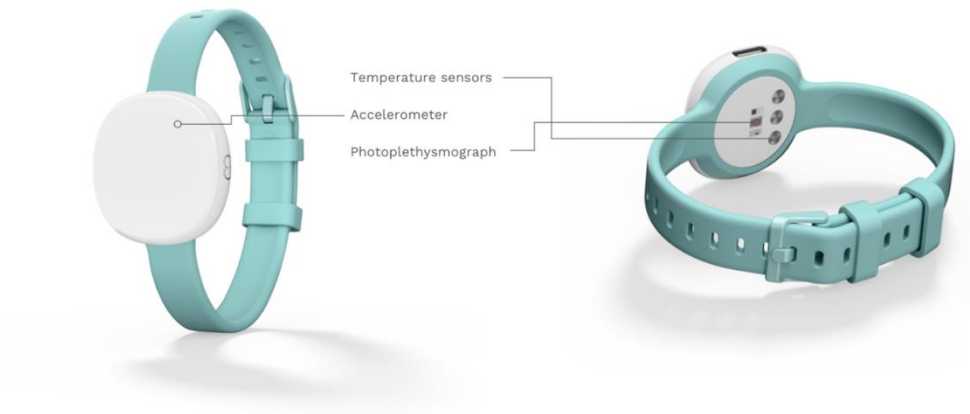
On the other end of the spectrum, only wrist skin temperature and perfusion had low ICC's (0·01 and 0·05, respectively); said differently, a given participant's perfusion or temperature measurements over time were not more similar to each other than would be expected from a random selection of that same parameter across all participants. As perfusion did not show phase-based changes in COVID-19 infection (see Table 3), it may be that another unaccounted for factor contributes to outcome measurements. Neither the participant's own repeated measurements nor the disease trajectory appear to significantly influence a given night's perfusion data. In contrast, since wrist skin temperature significantly differed from baseline across all other phases of a COVID-19 infection (see Table 3), it appears that the disease itself contributes more to a given night's temperature readings than the stability in a participant's own repeated measurements; almost all of the observed variance in nightly skin temperature occurs due to within participant differences (e.g., changes in their physiology over the course of the infection). Examining ICC values for each physiological parameter of interest provides greater context into the relative effect of potential phase-based changes in outcome variables as well as the residual variance attributable to the participant themselves.

Supplementary Tables and Figures

Supplementary Table S1. Intraclass correlation coefficients (ICCs) calculated based on the variance estimates for random effects of the null models predicting each of the seven physiological parameters of interest**.**

Predictors	Between Participant Variance (SD)	Variance of the Residuals (SD)	ICC
Wrist Skin Temperature	0·34 (0·59)	35·65 (5·97)	0·01
Heart Rate	43·59 (6·60)	13·53 (3·68)	0·76
Heart Rate Variability (SDNN)	121·64 (11·03)	36·08 (6·08)	0·77
Heart Rate Variability (RMSSD)	82·08 (9·06)	33·79 (5·81)	0·71
Heart Rate Variability Ratio	1·16 (1·08)	0·40 (0·63)	0·74
Respiratory Rate	4·48 (2·12)	0·64 (0·80)	0·88
Skin perfusion	3·8 e-05 (0·01)	6·75 e-04 (0·03)	0·05

Supplementary Figure S1. The Ava Fertility Tracker contains three sensors (temperature, accelerometer and photoplethysmograph) that measure wrist skin temperature, heart rate, respiratory rate, heart rate variability and skin perfusion simultaneously.



Study protocol

The study protocol can be downloaded here.

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Observational study employing a Medical Device

Clinical Study Protocol

Defining the role of a fertility bracelet for early recognition and monitoring of COVID-19 in Liechtenstein: an observational study (COVI-GAPP)

SHORT TITLE: A fertility tracker for recognition of COVID-19

Study Type:	Clinical trial with Medical Device (MD)
Study Categorisation:	Risk category according to HRA (A)
Study Registration:	Intended registry: International Standard Randomised Controlled Trial Number (ISRCTN) registry The study is conducted in Liechtenstein
Study Identifier:	N/A
Sponsor-Investigator	Prof.Dr.med. Lorenz Risch, PhD MPH MHA, labormedizinisches zentrum Dr. Risch, Wuhrstrasse 14, 9490 Vaduz, Liechtenstein, email lorenz.risch@risch.ch; Phone +41 58 523 3000; Mobile Phone +41 79 642 71 70
Investigational Product:	AVA bracelet
Protocol Version and Date:	**(SPIRIT #3)** Version 1.1 from 6.4.2020 replaces version 1.0 from 5.4.2020

PROTOCOL SIGNATURE FORM

Study Title	Defining the role of a fertility bracelet for early recognition and monitoring of COVID-19 in Liechtenstein (COVI-GAPP)
Study ID	NA

The Sponsor-Investigator has approved the protocol version 1.2 (dated 09/04/2020) and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements in Liechtenstein.

Sponsor-Investigator:

Name: Prof. Dr.med. Lorenz Risch, PhD MPH MHA

Date: Vaduz, 09/04/2020 Signature:

TABLE OF CONTENTS

GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
SAE	*Serious Adverse Event*

1 STUDY SYNOPSIS

Provide a structured synopsis containing all important information, preferably in tabular view:

Sponsor-Investigator	Prof.Dr.med. Lorenz Risch, PhD MPH MHA, labormedizinisches zentrum Dr. Risch, Wuhrstrasse 14, 9490 Vaduz, Liechtenstein, email lorenz.risch@risch.ch; Phone +41 58 523 3000; Mobile Phone +41 79 642 71 70
Study Title:	Defining the role of a fertility bracelet for early recognition and monitoring of COVID-19 in Liechtenstein (COVI-GAPP)
Short Title / Study ID:	A fertility tracker for recognition of COVID-19
Protocol Version and Date:	Version 1.1 (dated 06/04/2020)
Trial registration:	Intended registry: International Standard Randomised Controlled Trial Number (ISRCTN) registry
Study category and Rationale	Category A according to ClinO Art 20. The fertility tracker has a CE-mark, in the intended use, it is stated by means of the fertility tracker, "parameters are collected to improve the quality of the prediction and to provide general information on health and wellness". The fertility tracker employs non-invasive nightly monitoring of temperature, breath rate, pulse rate, and movements during sleep.
Clinical Phase:	Phase of development an algorithm for early recognition and monitoring of COVID-19
Background and Rationale:	Nightly monitoring of temperature, breath rate, pulse rate, movement by means of the AVA bracelet originally intended for cycle tracking in women. Whereas temperature is a sign of inflammation, breath rate can be regarded in function of affected airways, heart rate variability can be regarded as a marker of stress. All these parameters are expected to be altered in COVID-19 infection. From the measurements, algorithms for early prediction of COVID-19 will be developed. Risk for participants is low (non-invasive monitoring and blood sampling) the expected benefit is large, as algorithms trained on the obtained data recordings are expected to recognize COVID-19 earlier than clinical symptoms. The latter would allow for earlier isolation and stratification as well as monitoring of COVID-19 affected patients preventing further spread and allowing for appropriate healthcare.
Objective(s):	Primary objective A.) To see whether the AVA bracelet is capable to reliably identify persons with COVID19 infection early, before they get clinically. This would allow for early isolation and testing of contact persons, thereby preventing extensive spreading of the Virus. When reversing the process of lockdown of social and economic systems or during a so called second wave of the COVID-19 pandemic, the AVA bracelet could serve as a sensitive tool to observe relapsing infection rates. Secondary objective a.) To see whether the AVA bracelet would serve to recognize severe cases early allowing for risk stratification, early treatment and allocation of adequate care to patients with COVID19. b.) To obtain a seroprevalence of COVID19 affected cases in the population of Liechtenstein.
Outcome(s):	Occurrence of COVID-19 infection, Severity of COVID-19 infection.
Study design:	Observational population-based cohort study employing a CE-marked medical device.
Inclusion / Exclusion criteria:	Inclusion criteria: participant of the GAPP study. Exclusion criteria: Inability to provide informed consent.

Measurements and procedures:	Serological status for SARS-CoV2-antibodies will be determined at the beginning and the end of the study. The participants will be asked to answer a questionnaire about recent infections at study entry, undergo baseline serological testing. Study participants will be monitored overnight with the employed fertility tracker. We will collect information about clinically documented infections in all participants during follow-up, and provide serology at the end of the study. The study and participant recruitment will be performed within the study organization of the GAPP study, an ongoing prospective follow-up study. Baseline characteristics and other clinical information will be used from the GAPP study database.
Study Product / Intervention:	The fertility tracker automatically saves physiological information every 10 seconds throughout the night, requiring at least 4 hours of relatively uninterrupted sleep each night to stabilize parameter measurements. The wrist-worn bracelet acts as a data logger, recording and storing user's physiological sensors signals as raw datasets throughout the night. Currently, the user synchronizes the bracelet to the mobile phone application the following morning. It is planned that participants wear the fertility tracker overnight during the study period.
Control Intervention (if applicable):	Not applicable
Number of Participants with Rationale:	Participants of the ongoing population based GAPP cohort study conducted in Liechtenstein will be included (n=2170; study approved by KEK ZH Stv.-Nr. 66/09). These will receive the AVA bracelet for free. We eventually might attain a sample size of 5000 participant by onboarding additional participants. For this second phase, we will seek separate ethical approval.
Study Duration:	The course of the pandemic can currently not be predicted and is critical for the duration of the study. WE anticipate a duration of nearly 3 years.
Study Schedule:	Participants should be included as fast as possible, in order to catch as many endpoints during the COVID-19 pandemic. Planned 12/04/2020 of First-Participant-In Planned 31/12/2021 of Last-Participant-Out Depending on the course of the pandemic, the study can be terminated earlier.
Investigator(s):	Prof. Dr.med. David Conen, McMaster University, Hamilton (conend@mcmaster.ca), Dr.med. Martin Risch, Private University Liechtenstein, Triesen (martin.risch@risch.ch), Dr. Stefanie Aeschbacher, Universität Basel (stefanie.aeschbacher@usb.ch) , Kirsten Grossmann MSc, Private University Liechtenstein (kirsten.grossmann@risch.ch) , Dr.Maureen Cronin, MD PhD, Chief medical Officer AVA for women (maureen.cronin@avawomen.com)
Study Centre(s):	Single-centre study. GAPP-Studie c/o labormedizinisches zentrum Dr. Risch, Wuhrstrasse 14, 9490 Vaduz
Statistical Considerations:	Prediction of the development of COVID-19 infection will be modeled on the base of nightly monitoring of temperature, breath rate, pulse rate and movements by means of machine learning methods. Algorithms will be trained by comparing monitoring data of COVID-19 diseased and non-diseased individuals by a big data approach employing machine learning. The project partner AVA for women has already used such an approach to predict fertile days in women with a higher than 90% accuracy. The seroprevalence of COVID-19 will be presented as count (percentage) and we will standardize these numbers to the general population of the Principality of Liechtenstein. The sample size is given by the sample size included in the GAPP study.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ISO EN 14155 as well as all national legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

The WHO has declared the current coronavirus (COVID-19) outbreak to be a pandemic and therefore a Public Health Emergency of International Concern. It is crucial to rapidly gain a better understanding of the newly identified virus, especially in relation to potential clinical and public health measures that can be immediately used to improve patients' health and/or contain the spread of COVID-19. In particular, development of early and reliable detection of COVID-19 carriers and symptomatic individuals suspected of COVID-19 infection is needed. We are proposing to test the utility of a CE marked, marketed medical device that can continually track changes in physiological parameters in detecting early signs of a COVID-19 infection. In particular, the device's ability to register increases in physiological parameters associated with fever (e.g., resting pulse rate, breathing rate, and skin temperature) could render it an ideal candidate during screening point of care (POC), both for potential COVID-19 infections in asymptomatic, exposed users and asymptomatic users unsure of their exposure status.

This proposal aims to optimize efficient patient management, public health preparedness, and response to current and future outbreaks of COVID-19 infection; leveraging an existing medical-grade technology may allow clinicians and researchers to more rapidly evaluate patients' wellbeing, thereby enabling faster case detection. Additionally, healthcare professionals and researchers may benefit from using this device to monitor patients with confirmed cases of COVID-19. Synced to a central app via Bluetooth, the device measures physiological parameters continuously while the user sleeps; its design inherently alleviates the need for healthcare professionals to take the patient's temperature, breathing rate and pulse rate. We believe that, by reducing the in-person contact between patients and their care team, the AVA bracelet could also lower potential transmission rates among nurses, doctors, and/or researchers studying COVID-19's development [1]. This medical device is able to measure skin temperature, pulse rate, and breathing rate simultaneously, and thus may prove helpful in combatting a public health crisis through its potential to rapidly detect novel COVID-19 cases and enable remote surveillance of .

Studies on COVID-19, including one conducted by the World Health Organization's Joint Mission with China, reported that fever (87.9% of cases), dry cough (67.7% of cases), and shortness of breath (18.6% of cases) are the most frequent presenting symptoms [2-4]. Close to half (44%) of infected Chinese patients reported to treatment centers with fever as their first presenting symptom [2]. Our proposal is to test the utility of a CE-marked, marketed, wrist-worn medical device (AVA bracelet) that tracks breathing rate, pulse rate, skin temperature, heart rate variability and skin perfusion to generate data on potential early signs of COVID-19 in users at home [1]. While not specific to COVID-19, during a fever, body temperature and pulse rate increase [5-7] and shortness of breath can be measured by increased breathing rate. In a person with a known COVID-19 exposure, these signs could be indicative of an infection and helping with triaging for medical care [5]. A recent paper examining the validity of wrist temperatures compared to forehead and tympanic temperatures among Chinese COVID-19 patients found less overall variability in wrist temperatures [5].

The authors assessed individuals' temperatures upon their arrival to the medical clinic, demonstrating the importance of reliable knowledge about patients' vital signs at time of triage. Our research vision takes this finding a step further; what if, for example, healthcare professionals and doctors had patient-provided access to a record of their pulse rate, temperature, and breathing rate over the past week or month, measured by a regulatory-approved medical device? Could this help expedite triaging and lead to more data-informed decisions around identifying potential cases for reference to a medical setting where they could receive official diagnosis and treatment? Alternatively, a study could also probe the utility of the AVA bracelet as a remote continuous measurement device, worn during sleep to monitor for potential infection in exposed or high-risk populations in self-isolation at home. These are just some of the initial research questions we have identified as potential applications for the AVA bracelet; collaborative scientific inquiry and further proposals are welcome, as we consider how to best enlist our medical device in the management of COVID-19.

The AVA bracelet automatically saves physiological information every 10 seconds throughout the

night, requiring at least 4 hours of relatively uninterrupted sleep each night to stabilize parameter measurements [1]. The wrist-worn bracelet acts as a data logger, recording and storing user's physiological sensors signals as raw datasets throughout the night. Currently, the user synchronizes the bracelet to the mobile application the following morning. The mobile app reads the raw datasets via Bluetooth Low Energy (BLE) and transfers them to the backend. After computation and preprocessing of the physiological parameters based on the bracelet's recordings, an algorithm obtains pre-processed physiological parameters changes that are transferred back to the mobile app and displayed to the user.

Rapid action is required current the ongoing pandemic. The GAPP study is ideally suited to function as a platform to test the AVA device in a population with a high exposure to COVID-19 viruses and a high prevalence of testing [8]. GAPP is ongoing and therefore this project can be launched in a very short time period.

The intervention of observing study participants with the AVA bracelet, a medical device, together with planned blood drawings entails only minimal risks and burdens and, according to ClinO Art 20. can be categorized as category A.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

We hypothesize that by monitoring temperature, breath rate, pulse rate, and movements, it is possible to predict the occurrence of COVID-19 infection. We hypothesize, that temperature will increase due to inflammation/infection, breath rate will increase due to subclinical affection of lungs by COVID-19, heart rate variability as an indicator of stress will be diminished both as a consequence of infection also reflecting severity of infection. Further, we anticipate that registration of characteristic movements also allows to recognize cough. Fever, breathing problems, and cough are all clinical cornerstones in the diagnosis of COVID-19 infection. WE further hypothesize that the alterations in measured parameters antecede the occurrence of clinical symptoms.

Primary objective

A.) To see whether the AVA bracelet is capable to reliably identify persons with COVID19 infection early, before they get clinically. This would allow for early isolation and testing of contact persons, thereby preventing extensive spreading of the Virus. When reversing the process of lockdown of social and economic systems or during a so called second wave of the COVID-19 pandemic, the AVA bracelet could serve as a sensitive tool to observe relapsing infection rates.

Secondary objective

a.) To see whether the AVA bracelet would serve to recognize severe cases early allowing for risk stratification, early treatment and allocation of adequate care to patients with COVID19.

b.) To obtain a seroprevalence of COVID19 affected cases in the population of Liechtenstein.

3.2 Primary and secondary endpoints

Primary endpoint is the occurrence of COVID-19 infection, as assessed by clinical signs, serology and/or RT-PCR testing Date of occurrence, clinical symptoms and laboratory results, how infection was diagnosed is collected to describe the primary endpoint.The endpoints will be collected by periodic reports obtained on questioning the study participants. Participants and the

treating healthcare institutions will be contacted to obtain respective information.

As a secondary endpoint severity of COVID-19 infection will be assessed. Participants and the treating healthcare institutions will be contacted to obtain respective information. The following parameters will be collected: Hospitalization needed within 30 days of COVID-19 diagnosis (including timing)? ICU admission within 30 days of COVID-19 diagnosis (including timing)? Use of mechanical ventilation within 30 days of COVID-19 diagnosis (including timing)? Participant reported health status after COVID-19 diagnosis (including timing)? COVID-19 related mortality? Quantiative RT-PCR results (viral loads) and quantitative Immunoassay results of COVID-19 specific laboratory markers? Results of other respiratory pathogens in COVID-19 negative participants available? Further healthcare contact of patients tested negative for COVID-19?

3.3 Study design

This is a prospective cohort study employing a medical device (the AVA bracelet) as a monitoring tool. The GAPP study is already running since June 2010 and, after the baseline exam has been conducting follow-up visits every 3-5 years. Currently, the second follow-up period is being conducted. Due to the COVID-19 pandemic, the regular follow-up has been suspended. The study collective is very well described.

3.4. Study intervention

As soon as possible after ethical approval (within 1 week), study participants are offered an AVA bracelet. They will be asked to wear the AVA bracelet during the night until the study will be terminated. Temperature, breath rate, pulse rate and movings are recorded. Information on COVID-19 specific health status is collected at study start and symptomatic patients will be diagnosed for COVID-19, as recommended by national guidelines. At the end of the study blood will be drawn for serological analysis of anti-SARS-CoV2 antibodies.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

The GAPP study is a population based national cohort including 2170 study participants aged 25 to 41 at baseline. This number relates to about 32% of the whole population. Since the study was started to enrol participants from 2010, the study participants are now 35 to 51 years old [8].

The GAPP study (study homepage www.blutdruck.li) is an ongoing national cohort study done in the principality of Liechtenstein with a cooperation from the University Basel, Private University Liechtenstein, McMaster University Hamilton, and the labormedizinische zentrum Dr. Risch in Liechtenstein. Between 2010 and 2014 all inhabitants of Liechtenstein aged 25-41 years old were asked to participate in the study, and 2170 could be enrolled. The aim of the study is to identify the determinants for the development of hypertension and other cardiovascular risk factors. A large number of baseline characteristics and health information was collected in all participants. Several blood, urinary and genetic markers were collected. By ongoing follow-up we collect information on changes in health information and other characteristics are collected. Currently the second follow-up cycle is ongoing.

GAPP is very well established scientifically. More than 30 scientific manuscripts have been published so far, some of them in major international journals [8-41]. Therefore, the quality of the data collection is well recognized. In summary, the GAPP study provides a unique platform that would allow rapid evaluation of a promising medical device that has the potential to alleviate the suffering through the current COVID-19 pandemic.

The choice of the study population is ideal, as the organization is already in place, the study participants are already enrolled. With such a setting, the important and urgent study question can be addressed immediately.

Inclusion criteria:

- Participant of the GAPP study
- Providing consent to the present study

Exclusion criteria:

- Inability to provide informed consent

It is not planned to include vulnerable participants into the study.

After a first phase of including participants from the GAPP-study, we eventually might attain a sample size of 5000 participant by onboarding additional participants. For this second phase, we will seek separate ethical approval.

4.2 Recruitment, screening and informed consent procedure

The GAPP study department harbors 6 collaborators performing the study visits of the study participants onsite at the GAPP study facility (Wuhrstrasse 14) in Vaduz, Liechtenstein. The department has 4 consultation rooms and 3 office rooms. The proximity to the consultation rooms of the labormedizinische zentrum Dr. Risch allows for rapid scale-up of activities. Since the study is up and running and has a very good reputation within the study cohort and the whole country, starting the evaluation of the AVA watch in the COVID-19 pandemic is readily available. According to the world rankings, Liechtenstein is one of the countries with the highest incidences of COVID-19 (1582 cases per million persons, first case 2. March 2020), but on the other hand also has one of the highest testing frequencies for SARS-CoV-2 (2.75 percent of the whole population tested by March 29th 2020). Proximity of laboratory and study center, nationwide coverage of laboratory analysis, running national cohort, international cooperation, government support are all success factors for the envisaged project.

Participants already provided informed consent for participation in the GAPP study. As the study organization has an up-to-date address database, study participants are contacted by letter, email or telephonically. They will receive the participant information and called in into the study center upon stating their will to participate, where the AVA bracelet will be distributed. They will be offered opportunity to ask questions before providing informed consent by telephone, email, or at the occasion of device distribution, namely before the AVA bracelet will be distributed.

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The time between obtaining the study information and starting the distribution of AVA bracelets is at least 1 day.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. The consent form will be signed and dated by the investigator or his designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant, if requested. The consent form will be retained as

part of the study records. The informed consent process is documented in the participant database and any discrepancy to the process described in the protocol must be explained. No compensation is offered to study participants. They can keep the AVA bracelet after terminating the study.

4.3 Study procedures

The study starts as soon as ethical approval is obtained, preferably in calender week 15 2020. The rapid study start is intended in order to capture as many COVID-19 cases as possible. The study will be ongoing until the COVID-19 pandemic is eradicated, a vaccine or curative therapy has become available, or if the Investigators come to the decision to terminate the study. Due to the unclear course of the pandemic, it is not possible to provide an exact date of study duration. We anticipate that the study should be terminated on 31st December 2021 the latest.

First, study participants will be contacted by mail with the study information and the informed onsent sheet. After providing informed consent (in case of questions, the study staff can be contacted for questions at the contact information already known to the study participants) the study participants, baseline clinical information is provided in a study questionnaire. The study participants will then obtain an AVA bracelet, either by post or in the study center. Informed consent will be discussed personally on the occasion of a personal contact due to provision of the AVA bracelet or presentation for blood sampling.

While the AVA Bracelet was designed to measure physiological changes across the menstrual cycle. its sensors work across genders and age groups. We foresee that the device is capable of providing relevant insights for men and women alike during this pandemic, including among those populations most at risk of developing serious complications from COVID-19, including: people over the age of 60 and people with underlying conditions like hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer. The AVA bracelet automatically saves physiological information every 10 seconds throughout the night, requiring at least 4 hours of relatively uninterrupted sleep each night to stabilize parameter measurements. The wrist-worn bracelet acts as a data logger, recording and storing user's physiological sensors signals as raw datasets throughout the night. Currently, the user synchronizes the bracelet to the mobile phone application the following morning. The mobile app reads the raw datasets via Bluetooth Low Energy (BLE) and transfers them to the backend. After computation and preprocessing of the physiological parameters based on the bracelet's recordings, an algorithm obtains pre-processed physiological parameters changes that are transferred back to the mobile app and displayed to the user.

Designed to combine multiparameter measurement into one device, the AVA bracelet could leverage its real-time monitoring system to fight a novel health threat. We believe the simple but continuous monitoring of temperature, breathing and pulse rates could provide guidance around if and when people should seek medical care. Furthermore, the recorded physiological data could improve our knowledge of COVID-19's early signs and overall trajectory.

Figure 1: Illustration of the AVA bracelet

The AVA bracelet is intended to monitor a woman's fertility by measuring and recording physiological parameters (body temperature, resting pulse, heart rate variability, and breathing rate) as an aid in ovulation prediction to aid in conception (not to be used for contraception). Its intended use is to measure and display physiological parameters to aid women in ovulation prediction to facilitate conception. Additionally, parameters are collected to improve the quality of the prediction and to provide general information on health and wellness. The device is CE-marked (certificate see Appendix 2).

We will obtain COVID-19 specific information at baseline and study participants will asked to provide COVID-19 specific symptoms during the study duration. In case of the occurrence of COVID-19 specific symptoms, participants will be asked to undergo RT-PCR and serological testing according to national guidelines by utilizing routine healthcare. We will conduct periodic surveys (e.g. every 14 days) requesting the study participants to provide information regarding their health status. Study participants will be asked to provide a blood sample at the end of the study for serological studies of COVID-19 (investigation of SARS-CoV2-antibodies). The flowchart of the participant journey within the present investigation is summarized in Figure 2. A summary of the study visits is provided in Appendix 1.

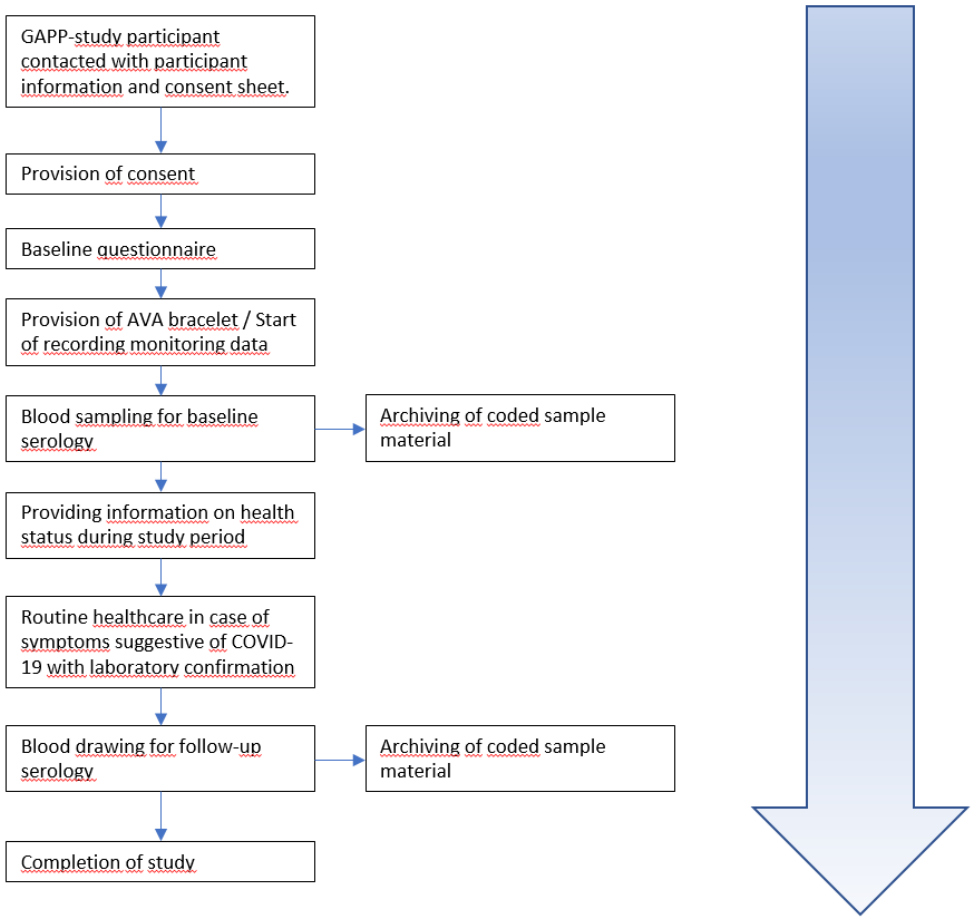

Figure 2: Journey of study participants.

4.4 Withdrawal and discontinuation

If a study participants withdraw from the study, recording of AVA bracelet data will be stopped. Data is stored in a coded manner and the decoding information for concerned individuals will be

irreversibly destroyed.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Together with Dr. Maureen Cronin and her team, data will be analysed by machine learning procedures. By training models, we aim to identify characteristic patterns of the recorded physiological parameters in order to predict the occurrence of COVID-19 infection. We intend to employ software packages such as R or SAS for modeling.

The present study is an (non-funded) associated partner to the COVID-RED consortium, which applied for a Horizon 2020 grant (see grant application as a document accompanying the present study protocol. Depending on the realization of that project, we will contribute data to that joint project.

The sample size of 2170 is given by the already existing study population. At a later stage, we may think of enlarging the sample size to 5000 by offering non-GAPP participants a participation in the study. However, this would be subject of a protocol amendment.

5.2. Handling of missing data and drop-outs

Should participants not regularly record data with the AVA bracelet, cases will be excluded from further analysis.

6 REGULATORY ASPECTS AND SAFETY

Device deficiencies and all adverse events (AE) including all serious adverse events (SAE) are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure. As only non-invasive monitoring is performed during the study period, no safety follow-up period is needed. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure [ISO 14155, 6.4.1.].

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ISO 14155, the HRA as well as other locally relevant legal and regulatory requirements.

6.1.1 Foreseeable adverse events and anticipated adverse device effects

Due to the non-invasive nature of the monitoring, the likelihood for foreseeable adverse events and the occurrence of anticipated adverse device effects is low. The most likely reason for an anticipated adverse device effect is a dysfunctional device making registration of monitoring data impossible.

6.1.2 Definition and Assessment of safety related events

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the investigational medical device.

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].
This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Event (SAE) [European regulation on medical devices 2017/745, art. 58].
Any adverse event that led to any of the following:
(a) death,
(b) serious deterioration in the health of the subject that resulted in any of the following:
(i) life-threatening illness or injury,
(ii) permanent impairment of a body structure or a body function,
(iii) hospitalisation or prolongation of patient hospitalisation,
(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
(v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are submitted to the EC via BASEC within 7 days. A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

Device deficiency
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

Health hazards that require measures
Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants SAE [ClinO Art. 37].

Causal Relationship of SAE [MEDDEV 2.7/3 revision 3, May 2015].
A causal relationship towards the medical device or study procedure should be rated as follows:
- Not related: The relationship to the device or procedures can be excluded.
- Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause.
- Causal relationship: The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Device deficiencies that might have led to an SAE are always related to the medical device.

6.1.3 Reporting of Safety related events

Reporting to Sponsor-Investigator:

All SAEs, device deficiencies and health hazards that require measures are reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event. Device deficiencies are assessed regarding their potential to lead to an SAE.

Pregnancies

Depending of the study, reporting of pregnancies is not necessary.

Reporting to Authorities:

In Category A studies, the sponsor is subject to the notification requirements specified in Art. 15 of the MedDO of 17 October 2011 (SR 812.213).

It is the Investigator's responsibility to report to the Ethics Committee via BASEC device deficiencies that could have led to serious adverse events if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate within 7 days [ClinO Art. 42].

Health hazards that require measures are reported to the Ethics Committee via BASEC within 2 days [ClinO Art. 37].

Periodic safety reporting:

A yearly safety update-report is submitted by the Investigator to the Ethics Committee via BASEC.

A report is submitted to the Amt für Gesundheit of the Principality of Liechtenstein by the Sponsor-Investigator, as defined in Art. 15a,b of the MedDO of 17 October 2011 (SR 812.213).

6.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

6.4 Radiation

Use of the device is not subject to radiation.

6.5 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of substantial changes is also available on www.swissethics.ch.

A list of all non-substantial amendements will be submitted once a year to the competent EC together with the ASR.

6.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely before 31st December 2021,

- When the COVID-19 pandemic is eradicated,
- A vaccine or curative therapy has become available

- Insufficient compliance of the study participants to the study protocol
- Due to ethical concerns,
- Due to insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice occure that make the continuation of the study unwise
- Early evidence of harm or benefit of the observations with the AVA bracelet

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

The www.swissethics.ch template concerning the notification of completion, discontinuation or interruption of the clinical trial is used for this purpose.

Health-related data at the end of the study are introduced into the GAPP study database.

6.8 Insurance

In the event of study-related damage or injuries, the liability of the institution labormedizinisches zentrum Dr. Risch in Vaduz provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

The expected scientific value is expected to be large considering the threat of the pandemic and the need for earliest possible identification of COVID-19 affected cases. The methodology chosen is ideal: it is based on a study already in operation, with funding already obtained, a bracelet already approved and in use for fertility tracking, ready to start immediately. No vulnerable individuals will be included.

7.2 Risk-benefit assessment

Risk for participants is low (non-invasive monitoring and blood sampling). The expected benefit is large, as algorithms trained on the obtained data recordings are expected to recognize COVID-19 earlier than clinical symptoms. The latter would allow for earlier isolation and stratification as well as monitoring of COVID-19 affected patients preventing further spread and allowing for appropriate healthcare.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Study personnel trained on all important study related aspects is employed for conducting the study. Once yearly, an independent audit is done by Prof. Dr. Christoph Saely from the Vorarlberg Institute of Vascular Investigation and Treatment.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

The GAPP study employs secuTrial and MOLIS to record data. Both systems have audit trails. For each participant a CRF is maintained. CRFs are identified by coded information used in the GAPP study. Further, the source data of the AVA bracelets is recorded within the computer systems of AVA. These data are kept strictly confidential and cannot be changed.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number. Access to computer systems is highly restricted by two-level passwords. Access on data is recorded in a traceable manner. Data is backed up at the data center of the labormedizinisches zentrum Dr. Risch in Vaduz.

Biological material in this study is not identified by participant name but by a unique participant number. Biological material is appropriately stored at -80°C in a restricted area only accessible to the authorised study personnel at the GAPP-study and the labormedinisches zentrum Dr. Risch.

8.4 Retention and destruction of study data and biological material

All study data and biological material are archived at the labormedizinisches zentrum Dr. Risch in Vaduz for 10 years after study termination or premature termination of the study. After the study sera will be destroyed according to the normal process within the ISO-17025 accredited labormedizinisches zentrum Dr. Risch.

9 MONITORING AND REGISTRATION

The external auditor Prof. Dr.Christoph Saely will be conducting a monitoring visit before starting the present study and once yearly.

It is intended that the study will be registered in the Intended registry: International Standard Randomised Controlled Trial Number (ISRCTN) registry.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The study is funded by the government of the principality of Liechtenstein (75000 CHF), the prince of Liechtenstein (350'000 CHF) and the Hanela Stiftung Aarau (100'000 CHF). Further funding will be sought. The funding sources did not have any role in conceiving the study idea, planning of the study, and will not have any role in the decision to publish. It is planned to publish the study data in peer reviewed scientific journals. Decision to publish will be done by a majority of

investigators. Authorship will be clarified according to the ICMJE-criteria. Aggregate data will be provided upon request to qualified external research proposals. Dr. Maureen Cronin is employee of AVA. All other investigators are independent of AVA.

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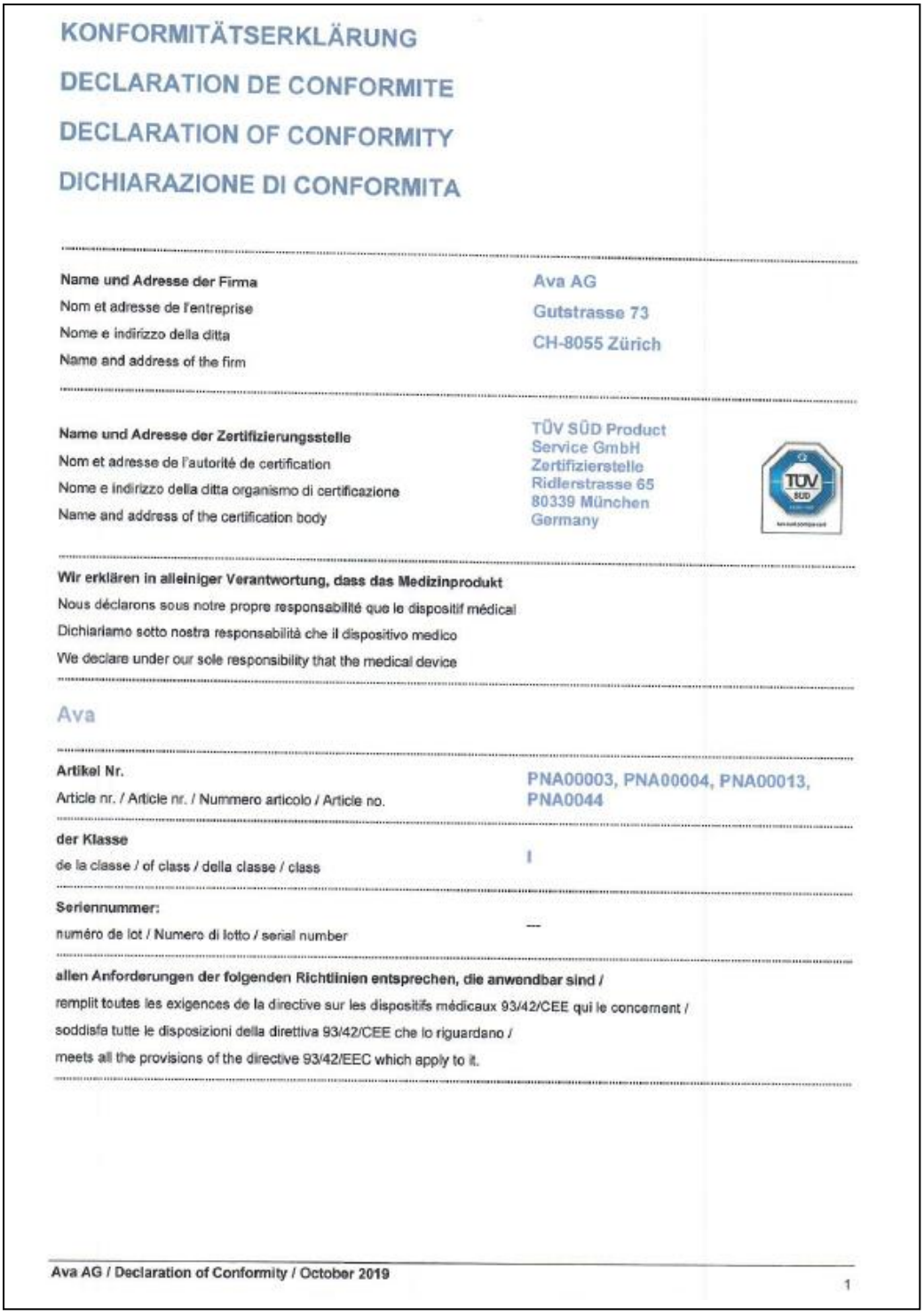
48. Ordinance on Clinical Trials in Human Research (ClinO) https://www.admin.ch/opc/de/classified-compilation/20121176/index.html

Appendix 1: Schedule of assessments

Time (hour, day, week)	>-1 day	0	Occurrence of symptoms	Periodic reporting (e.g. 14 days)	Final study visit
Visit	Information	Distribution of bracelet / provision of COVID-19 related information	Visit at occurrence of COVID-19 specific symptoms		Final study visit
Oral and written patient information	+				
Written consent		+			
Inclusion-/ exclusion criteria		+			
Medical history		+			
Participant characteristics		+			
Procedures			+		
Intervention		+	+		
Questionnaire		+	+	+	+
Sampling		+	+		+

Appendix 2: Declaration of conformity of the AVA bracelet.



KONFORMITÄTSERKLÄRUNG

DECLARATION DE CONFORMITE

DECLARATION OF CONFORMITY

DICHIARAZIONE DI CONFORMITA

Name und Adresse der Firma Nom et adresse de l'entreprise Nome e indirizzo della ditta Name and address of the firm	Ava AG Gutstrasse 73 CH-8055 Zürich
Name und Adresse der Zertifizierungsstelle Nom et adresse de l'autorité de certification Nome e indirizzo della ditta organismo di certificazione Name and address of the certification body	TÜV SÜD Product Service GmbH Zertifizierstelle Ridlerstrasse 65 80339 München Germany

Wir erklären in alleiniger Verantwortung, dass das Medizinprodukt
Nous déclarons sous notre propre responsabilité que le dispositif médical
Dichiariamo sotto nostra responsabilità che il dispositivo medico
We declare under our sole responsibility that the medical device

Ava

Artikel Nr. Article nr. / Article nr. / Nummero articolo / Article no.	PNA00003, PNA00004, PNA00013, PNA0044
der Klasse de la classe / of class / della classe / class	I
Seriennummer: numéro de lot / Numero di lotto / serial number	---

allen Anforderungen der folgenden Richtlinien entsprechen, die anwendbar sind /
remplit toutes les exigences de la directive sur les dispositifs médicaux 93/42/CEE qui le concernent /
soddisfa tutte le disposizioni della direttiva 93/42/CEE che lo riguardano /
meets all the provisions of the directive 93/42/EEC which apply to it.

Ava AG / Declaration of Conformity / October 2019 1

Angewandte harmonisierte Normen, nationale Normen oder andere normative Dokumente / Normes harmonisées, normes nationales et autres documents normatifs appliqués / Norme armonizzate o nazionali applicate, altri documenti normativi applicati / Applied harmonised standards, national standards or other normative documents	EN ISO 13485:2016 MDD 93/42/EG:2007 ISO 14971:2012 IEC 62304:2015 IEC 62366:2016 RED 53/EU 2014 IEC 60601-1-6 : 2015 ISO 10993-1, 5, 12, 18
Konformitätsbewertungsverfahren Procédure d'évaluation de la conformité Procedimentodi valutazione della conformità Conformity assessment procedure	93/42/EG, Annex II
Konformitätsbewertung gültig bis : Declaraction de conformite est valide jusqu'à : Declaration of conformity is valid until: Dichiarazione di conformita in vigore a:	May 26th, 2020
Ort, Datum / Lieu, date / Luogo, data / Place, date	**Name und Funktion** / Nom et fonction / Nome e funzione / Name and function
Zurich OCT 4 2019	Pascal Koenig CEO

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-13
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	21-25
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	21-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Investigation of the use of a sensor bracelet for the pre-symptomatic detection of changes in physiological parameters related to COVID-19: an interim analysis of a prospective cohort study (COVI-GAPP)

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Primary Subject Heading:	Global health

Secondary Subject Heading:	Public health, Immunology (including allergy), Infectious diseases, Global health
Keywords:	COVID-19, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, VIROLOGY, Public health < INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Investigation of the use of a sensor bracelet for the pre-symptomatic detection of changes in physiological parameters related to COVID-19: an interim analysis of a prospective cohort study (COVI-GAPP)

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ABSTRACT

Objectives We investigated machine learning based identification of pre-symptomatic COVID-19 and detection of infection-related changes in physiology using a wearable device.

Design Interim analysis of a prospective cohort study.

Setting, participants and interventions Participants from a national cohort study in Liechtenstein were included. Nightly they wore the Ava-bracelet that measured respiratory rate (RR), heart rate (HR), heart rate variability (HRV), wrist-skin temperature (WST), and skin perfusion. SARS-CoV-2 infection was diagnosed by molecular and/or serological assays.

Results A total of 1.5 million hours of physiological data were recorded from 1,163 participants (mean age 44 +/- 5.5 years). COVID-19 was confirmed in 127 participants of which, 66 (52%) had worn their device from baseline to symptom onset and were included in this analysis. Multi-level modelling revealed significant changes in five (RR, HR, HRV, HRV ratio, and WST) device-measured physiological parameters during the incubation, pre-symptomatic, symptomatic, and recovery periods of COVID-19 compared to baseline. The training set represented an 8-day long instance extracted from day 10 to day 2 before symptom onset (SO). The training set consisted of 40 days measurements from 66 participants. Based on a random split, the test set included 30% of participants and 70% were selected for the training set. The developed long short-term memory (LSTM) based recurrent neural network (RNN) algorithm had a recall (sensitivity) of 0.73 in the training set and 0.68 in the testing set when detecting COVID-19 up to two days prior to symptom onset.

Conclusion Wearable sensor technology can enable COVID-19 detection during the pre-symptomatic period. Our proposed RNN algorithm identified 68% of COVID-19 positive participants two days prior to symptom onset and will be further trained and validated in a randomized, single-blinded, two-period, two-sequence crossover trial.

Study registration ISRCTN51255782.

Strengths and limitations of this study

- Large sample size from a well-characterized and healthy national cohort.
- Wearable device technology combined with machine learning to monitor health parameters related to early detection of COVID-19 infections.
- Solely data from laboratory confirmed COVID-19 infections were used.
- Data from one single study centre may limit the generalizability of our findings.
- Small subsample of COVID-19 positive cases with sufficient high-quality data.

INTRODUCTION

One of the primary ways of controlling the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) involves identification, tracing, and isolation programs implemented in several countries [1]. With multiple SARS-CoV-2 variant strains emerging, countries have prioritised vaccine rollouts, searches for alternatives to quarantine, and identification of individuals with COVID-19. Reverse transcription-polymerase chain reaction (RT-PCR), serological testing, surveys, temperature measurements, and symptom checks are used to detect COVID-19 [2]. However, these methods are usually unable to identify pre-symptomatic or asymptomatic individuals.

Recent studies have highlighted the need to identify potential cases prior to symptom onset (SO) to prevent virus transmission [2,3]. Asymptomatic patients are likely to ignore safety precautions, leading to increased virus transmission. Detection of COVID-19 during the asymptomatic or pre-symptomatic stage facilitates early isolation, thereby limiting contact with susceptible individuals. Commonly reported COVID-19 symptoms include fever, coughing, chest tightness, difficulty breathing, fatigue, dyspnoea, myalgia, sputum production, headache, and gastrointestinal symptoms [4,5]. While molecular tests are continuously used to confirm infections, the logistics and costs of repeat tests across populations are prohibitive [6]. Recently, scientists have called for further research investigating whether wearable medical devices such as Ava-bracelets and direct-to-consumer products such as Fitbit [7,8], smartwatches [8,9] and other activity trackers [10] could be used for such surveillance [11].

Here, we assess the use of an existing regulated wearable medical device (Ava-bracelet) to analyse COVID-19-related changes in various physiological parameters across four infection-related periods: incubation, pre-symptomatic, symptomatic, and recovery. To our knowledge, this is the first prospective study to measure physiological changes in respiratory rate (RR),

heart rate (HR), heart rate variability (HRV), wrist-skin temperature (WST), and skin perfusion to develop an algorithm to detect pre-symptomatic COVID-19 infection.

METHODS

Study design and participants

Participants from the ongoing observational population-based prospective cohort study (Genetic and Phenotypic Determinants of Blood Pressure and Other Cardiovascular Risk Factors (GAPP); *n* = 2,170) in the Principality of Liechtenstein were invited to participate in the current study (COVI-GAPP) [11]. Active since 2010, the GAPP study was designed to understand the development of cardiovascular risk factors in the general population better (i.e. healthy adults aged 25 to 41 years) [12]. The exclusion criterion regarding participation in the COVI-GAPP study was individuals who did not provide written informed consent. The first COVI-GAPP participants were enrolled in April 2020, and the data used for this interim analysis was collected through March 2021 (*n* = 1,163). The local ethics committee approved the study protocol, and written informed consent was obtained from each participant (BASEC 2020-00786). This COVI-GAPP interim analysis was pre-planned as a pilot study to provide an initial algorithm for the COVID-RED project (n= 20,000), a randomised, single-blinded, two-period, two-sequence crossover trial [13].

Bracelet, app, and participant compliance

The Ava-bracelet (version 2.0; Ava AG, Zurich, Switzerland) is an FDA-cleared and CE-certified fertility aid bracelet that complies with international regulatory requirements and applicable standards [14,15]. The wrist-worn tracker is commercially available at US$ 279 and consists of three sensors that measure five physiological parameters simultaneously: RR (breaths per minute), HR (beats per minute), HRV (ms), WST (°C), and skin perfusion (Figure S1). Although the Ava-bracelet measures multiple forms of HRV, we focused on two time- and one frequency-dependent measurements: standard deviation of the normal-to-normal interval (SDNN), root mean square of successive differences (RMSSD), and HRV ratio (see Supplementary Materials). In addition to the physiological parameters of interest, the Ava-bracelet measures sleep quantity (duration) and sleep quality using a built-in accelerometer. Prior studies have demonstrated how device data can inform a machine-learning algorithm that detects ovulating women's most fertile days in real time with 90% accuracy [16]. Worn only while asleep, the Ava-bracelet saves data every 10 s and requires at least four hours of

relatively uninterrupted sleep. The participants synchronised their bracelets with a complementary smartphone app upon waking, transferring data from the device to Ava's backend system.

Although no study-specific adjustments were applied to the hardware of the Ava-bracelet, the complementary app had a customised user functionality developed by the manufacturer specifically for the COVI-GAPP study. Participants could still see and monitor changes in the physiological parameters in the app; however, they did not receive messages or algorithm-driven interpretations of their data (Figure 1A). Participants recorded behaviours that may have interfered with the physiological parameters of interest (e.g., alcohol, medication, and drug intake), as such substances can alter central nervous system functioning (Figure 1B) [17]. The daily diary in the custom app enabled participants to record COVID-19-related symptoms (Figure 1C). To ensure the highest quality data, the study team reviewed a weekly compliance log that indicated which participants had synced their Ava-bracelets with the app during the preceding week [18]. The study team followed up with the participants individually to mitigate operational challenges or log in issues.

SARS-CoV-2 antibody testing and RT-PCR testing

SARS-CoV-2 antibody tests were assessed at baseline (starting April 2020) and during follow-up (starting December 2020) by the medical laboratory Dr. Risch Ostschweiz AG (Buchs SG, Switzerland). The tests were assessed with an orthogonal test algorithm that employed electrochemiluminescence assays. These assay test for pan-immunoglobulins directed against the N antigen and the receptor-binding domain of the SARS-CoV-2 spike protein [19]. Seroconversion was assumed if the first blood sample was negative for SARS-CoV-2 antibodies, and the second sample was positive.

If participants had any symptoms during the study period, they were encouraged to visit the Liechtenstein National Testing Facility for RT-PCR testing. The testing facility was open daily allowing for higher testing frequencies than that in other European countries [20]. RT-PCR was performed on either the COBAS 6800 platform (Roche Diagnostics, Rotkreuz, Switzerland) or the TaqPath assay on a QuantStudio 5 platform (Thermo Fisher Scientific, Allschwil, Switzerland) [20–22]. Participants diagnosed with COVID-19 contacted the study team to discuss their symptoms and health statuses. Additionally, participants provided their date of SO and overall symptom duration, enabling us to calculate the symptom end (SE) date.

Questionnaires

For the second antibody test, all participants were asked to complete a questionnaire providing personal information (age, sex), smoking status (current, past, never), blood group (A, B, AB, 0, unknown), number of children, exposure to household contacts who tested positive for COVID-19, working with people who have tested positive for COVID-19, and vaccination status. We calculated the body mass index (BMI) based on the height and weight collected from the GAPP database.

Statistical analysis

The primary objective was to determine whether different physiological parameters deviated from the baseline during COVID-19 infection. This information was used to develop a model for predicting COVID-19 infection before SO. To evaluate whether RR, HR, HRV, WST, and skin perfusion deviated from baseline measurements during the four infection-related periods, we categorised the daily parameter measurements as occurring at baseline if the day (*d*) was >10 days prior to SO (i.e. $d > SO-10$), the incubation period as $SO-10 \leq d < SO-2$, and the pre-symptomatic period as $SO-2 \leq d < SO$. We chose a cut-off of -2 days based on previous reports of infected participants becoming contagious two days before symptom onset[23]. Because the participants' reported symptom durations varied, the measurements were categorised into the symptomatic infection category if $SO \leq d \leq SE$. Finally, the parameters collected after SE were classified as being in the recovery period ($d > SE$).

Development of a machine learning algorithm for detecting pre-symptomatic COVID-19 infection

We chose a recurrent neural network (RNN) with long short-term memory (LSTM) cells for the binary classification of an individual as healthy or infected (positive for COVID-19) on a given day. LSTM networks have proven to be highly accurate in recognising time series patterns and events across large datasets [24]. The internal structure of such networks can memorise states and easily fetch or activate them, even if they were created many epochs ago. The LSTM network we implemented consisted of two hidden layers with 16 and 64 cells (Figure 2). Its

output activation was a sigmoid function, whereas the recurrent activation was a hyperbolic tangent (tanh) function. The output was limited to a range between 0 and 1 to ensure that the model yielded an overall probability of infection on a given day. A potential COVID-19 infection was indicated when this probability exceeded 0.5.

1. Data processing and multi-level model specification

All data processing and analyses were performed in R (v3.6.1) and Python (v3.6). Pre-processing of the data was performed to remove potential artefacts and ensure consistency with best practices [25] (see Supplementary Materials for detailed description). Further, we ran a series of multilevel models with random intercepts and slopes to determine the differences in physiological parameters during the infection-related periods compared to baseline. Given our continuous criterion, we modelled our outcomes of interest using residual maximum likelihood estimation and Satterthwaite degrees of freedom. Four binary variables were created, indicating the infection period to which a given measurement belonged (1 = belonging to that period, 0 = not belonging to that period). The reference baseline-period measurements were encoded as zero across all four binary variables. The reported results included unstandardised regression coefficients for each effect. When multiple models were possible for the same parameter, we chose the model using the percentile of the data (stable maxima) with the best fit (see Supplementary Materials). To ensure a family-wise alpha level less than or equal to 0.05, we implemented Bonferroni correction for the seven analysed parameters (corrected alpha level of $p = 0.007$) and adjusted the definition of marginal significance accordingly (i.e. $0.007 \leq p \leq 0.05$).

2. Data preparation and feature extraction for algorithm development

The Ava-bracelet records over a million data points per use. Therefore, we first identified the features that are most predictive of COVID-19. We normalised the night-time WST, RR, and HR values to prime our model to detect deviations from baseline measurements and ensure greater stability in the measurements (e.g. to minimise inter-participant variability). Next, we compared the predictive performance of the raw features before engineering the novel composite features. We conducted a principal component analysis decomposition to test the correlation between the day of SO and other binary-labelled features (e.g. alcohol

consumption). We also examined the correlation between WST and other physiological parameters to determine the potential autocorrelation prior to the model specification.

3. Training process

To limit our analysis to symptomatic COVID-19 cases, participants had to report the date of SO and record at least 28 days of bracelet data prior to that date. The full four weeks of data were required to ensure accurate baseline readings and enable the algorithm to account for cyclical variations in parameters attributable to monthly hormonal changes. Thus, each participant included in the analysis had at least 29 consecutive days of data recorded using the bracelet. We partitioned the data into 8-day sequences, enabling the algorithm to compare the physiological parameters across 8-day windows. This means that each user had more negative (class 0; "healthy" days) sequences in the distribution (e.g., [26, 19], [25, 18] [11, 3]) than positive sequences (class 1; "infected" days [e.g., SO-10 to SO-2] as shown in Figure 3). We selected a binary cross-entropy loss function for the RNN by using a stochastic gradient descent (SGD) optimiser. Owing to the sample size, we set the learning rate to 0.007 and 2000 epochs, while also enabling an early stopping mechanism to prevent model overfitting. We trained our RNN ten times, randomly splitting our sample into a training set (70% of participants) and a test set (30% of participants) for each instance. We report the metrics of the best-performing RNN model selected according to the following recall equation:

$$overall\_recall = ((recall\_class\_1\_train + recal\_class\_0\_train) * 0.7 + (recall\_class1\_test + recall\_class\_0\_test) * 0.3)/2$$

Finally, because of the number of COVID-19 cases compared to healthy days in our dataset, we upsampled instances of class 1 through duplication, such that it was represented in our training set 1.15 times more than a given negative sequence (i.e. class 0). Thus, the SGD optimiser treated the two classes as roughly equal and no longer overweighted the importance of the parameters predicting a healthy 8-day period. By training this LSTM model, we sought to leverage deep learning to predict the pre-symptomatic onset of COVID-19.

Patient and public involvement

No patient or public involvement.

RESULTS

Participants

A total of 1,163 participants (mean age = 44.1 years, standard deviation [SD] = 5.6; 667 [57%] females) were enrolled in the COVI-GAPP study (Figure 4). Of these participants, 127 (10.9%; 95% confidence interval (CI) [9.3,12.8]) contracted COVID-19 during the study period. 10 infected participants were hospitalised for short-term monitoring, with breathing difficulties and fever as the main reported symptoms. Three asymptomatic infected participants were retrospectively identified using antibody tests. As seen in Table 1, there were no differences in the sex ratio, age, BMI, or smoking status between individuals who did or did not test positive for COVID-19 during follow-up (all *p*-values ≥ 0.30). A significantly higher proportion of participants who contracted COVID-19 reported household contacts (*n* = 58 of 1,036 seronegative participants vs. 53 of 127 seropositive participants; $p < 0.001$) or work colleagues who also had COVID-19 (*n* = 230 of 1,036 seronegative participants vs. 49 of 127 seropositive participants; $p < 0.001$). On average, COVI-GAPP participants wore the Ava-bracelet for 1,370.8 h over the course of the study (SD = 802.7), for a total of 1,453,006 h. Of the 127 participants who tested positive for COVID-19, either through RT-PCR and SARS-CoV-2 antibody tests or antibody tests only, 66 users had worn their bracelet at least 29 days prior to SO which enabled sufficient data quality. Among these 66 participants, COVID-19 infection was confirmed by RT-PCR test and SARS-CoV-2 antibody test (*n* = 48) or solely by antibody test (*n* = 18).

1. Participants with confirmed COVID-19

Table 2 shows the clinical characteristics of COVID-19 positive participants, stratified according to their compliance with wearing the Ava-bracelet prior to SO. A series of 26 analyses of variance and chi-square tests with Bonferroni correction revealed that only BMI varied significantly between the two groups; noncompliant participants had a higher mean BMI (25.8 kg/m^2, SD = 4.0) than their compliant peers (23.8 kg/m^2, SD = 3.7; $F(1, 116) = 10.39$, $p = 0.002$).

2. Compliant participants with confirmed COVID-19

Among the 66 compliant participants with COVID-19, 13,248 nights of data were collected (mean duration = 200 nights, SD = 47; range 72–284 nights) for a total of 124,079 h (mean

hours per participant = 1,880, SD = 461.8). The compliant participants had a mean age of 42.9 years (SD = 5.6), and most had never smoked (*n* = 57; 86%). Their COVID-19 symptoms lasted for an average of 8.5 days (SD = 5.0; range 1–25 days). Table 2 shows the frequency of the self-reported symptoms.

Physiological changes during the clinical course of COVID-19

Employing multilevel modelling, we observed significant changes in five (RR, HR, HRV, HRV ratio, and WST) of the seven device-measured physiological parameters during the incubation, pre-symptomatic, symptomatic, and recovery periods of COVID-19, compared to baseline. Table 3 lists the unstandardised coefficient values for each statistical model. The complete course of the different physiological parameters is shown in Figure 5.

1. Respiration rate

COVID-19 positive participants had a significantly higher RR during the symptomatic period than at baseline ($\beta_{intercept}$ = 15.1 breaths/min, standard error [s.e.] = 0.26; p <0.0001). Controlling for intra-individual variance, the nightly RR increased by 1.0 breaths/min (s.e. = 0.18; p <0.0001). There were no significant differences in the RR detected between the baseline and other periods (all $p \geq 0.114$).

2. Heart rate

At baseline, the participants had a resting nightly HR of 55.4 beats per minute (bpm; s.e. = 0.83; $p < 0.0001$). During the incubation period, individuals' HR increased significantly by 0.87 bpm (s.e. = 0.29; $p = 0.004$). HR remained elevated in the pre-symptomatic period, expected to be 1.0 bpm higher than that at baseline (s.e. = 0.36, $p = 0.007$). HR continued to increase following SO, beating 2.2 bpm faster than at baseline (s.e. = 0.48, $p < 0.0001$). Finally, even after SE, participants had a significantly elevated HR (+0.87 bpm higher than baseline; s.e. = 0.22, $p = 0.0002$).

3. Heart rate variability: standard deviation of the NN interval

Compared to a baseline SDNN of 59.6 ms (s.e. = 1.4, $p < 0.0001$), participants had significantly decreased SDNN in the incubation ($\beta_{incubation}$ = −1.5 ms, s.e. = 0.59, $p = 0.0149$), pre-

symptomatic ($\beta_{pre-symptomatic}$= −1.7 ms, s.e. = 64; p = 0.0086), and symptomatic ($\beta_{symptomatic}$ = −1.4 ms, s.e. = 0.73; p = 0.0499) periods. Following SE, SDNN returned to baseline levels ($\beta_{recovery}$ = −0.9ms, s.e. = 0.51, p = 0.0787).

4. Heart rate variability: root mean square of successive differences

Our analyses did not reveal any significant phase-based differences in RMSSD for COVID-19 positive participants during their infection (all $p \geq 157$) compared to baseline ($\beta_{intercept}$= 43.7 ms, s.e. = 1.2; $p \leq 0.0001$).

5. Heart rate variability ratio

As with SDNN, multilevel analysis revealed a marginally significant decrease in HRV ratio during the incubation ($\beta_{incubation}$ = −0.01, s.e. = 0.01; p = 0.0361) and pre-symptomatic periods ($\beta_{pre-symptomatic}$ = −0.02, s.e. = −0.01; p = 0.0165) compared to baseline ($\beta_{intercept}$ = 0.50, s.e. = 0.02; $p < 0.0001$). No significant difference in HRV ratio emerged between baseline and the symptomatic or recovery periods (all p-values ≥ 0.5474).

6. Wrist skin temperature

Over and above participant level variance, WST increased by 0.13°C (s.e. = 0.04; p = 0.001), 0.18°C (s.e. = 0.05; p = 0.001), and 0.3°C (s.e. = 0.05; $p < 0.0001$) during the incubation, pre-symptomatic and symptomatic periods, respectively, compared to baseline ($\beta_{intercept}$ = 35.3°C, s.e. = 0.06; $p < 0.0001$). WST remained elevated by 0.2°C relative to baseline, even during the recovery period (s.e. = 0.03; $p < 0.0001$).

7. Skin perfusion

No changes in skin perfusion were observed when comparing measurements during infection (all $p \geq 339$) with baseline values ($\beta_{intercept}$= −0.01, s.e. = 0.0; $p <$ 0001).

Model specification and algorithm performance

The best-performing RNN consisted of composite features derived from the maximum nightly WST and median nightly RR, averaged across the preceding three-night window. Other parameters were excluded. Table 4 summarises the model performance metrics for the training and testing samples. Class 1 represented an 8-day long training instance extracted from day 10 to day 2 before SO. Class 0 represented a training instance extracted from all other 8-day long consecutive measurements. The training set consisted of 40 days of measurements from 66 participants with a 70:30 train-test split. Sensitivity is reflected in the recall of Class 1, whereas specificity is determined by the recall of Class 0. Training the algorithm to detect COVID-19 one day before SO did not improve recall (data not shown).
In the test set, the algorithm detected 68% of COVID-19 cases two days prior to SO.

DISCUSSION

Our main objective was to assess the use of existing medical-grade technology in the early detection of changes in physiological parameters related to COVID-19, thereby facilitating early isolation and testing of potentially affected individuals to limit the spread of the SARS-CoV-2 virus. Our RNN algorithm, trained and tested using a 70:30 split, identified 68% of COVID-19 cases up to two days before SO in 66 participants with an accurate false-positive rate and laboratory-confirmed cases of SARS-CoV-2. Therefore, we demonstrated that a wearable sensor bracelet implemented alongside a machine-learning model has the potential to detect COVID-19 infections prior to SO.

Our research is one of the first prospective cohort studies using wearable sensor technology to gather real-time continuous physiological data upon which a machine learning algorithm for COVID-19 pre-symptomatic detection was trained. Previous studies have evaluated the use of different wearable devices and machine learning to identify COVID-19 infections based on self-reported COVID-19 infections [7-8,25–31]. Mishra et al. [9], for example, evaluated the use of resting HR data from 32 infected Fitbit users to detect COVID-19 cases in real time and identified 62.5% of the cases before SO. Similarly, Miller et al. [33] used RR, HR, and HRV data from 271 WHOOP strap wearers to identify 20% of participants who developed COVID-19 before SO and 80% by day three after SO.

Only laboratory-confirmed SARS-CoV-2 infections were used in this study to ensure more conclusive results. Our RNN algorithm detected 68% of laboratory-confirmed cases before SO, with additional statistical analyses revealing significant changes in the HR, HRV, and WST, across the disease trajectory. Furthermore, our algorithm included more concurrent physiological parameters than previous studies, such as nightly RR, WST, and cardiac data [7,9,31–35]. Unlike previous studies that performed retrospective measurements, our system could detect infections before SO. Uniquely, our research repurposed a previously existing CE-marked medical device for a novel purpose, illustrating a relatively inexpensive technique for detecting pre-symptomatic COVID-19.This machine-learning algorithm can be applied to any sensor device that measures the same physiological parameters.

Our findings suggest that a wearable-informed machine learning algorithm may serve as a promising tool for pre- or asymptomatic detection of COVID-19. However, RT-PCR testing remains the most effective method to confirm COVID-19 infections. A systematic review of wearable sensors in detecting COVID-19 reported these investigations as promising but also highlighted the need for investigations in broader populations [36]. Based on this interim analysis, a 20,000-person randomised controlled trial is underway to test the real-time efficacy of the RNN algorithm which can act on real-time machine-learning-driven alerts about the likelihood of a COVID-19 infection before symptoms are reported [13]. The initial results from this larger trial are expected in December 2022, with a wider validation and more practical implications of the first presented data approach. In addition, detecting other illnesses using wearable-informed machine-learning algorithm is promising [28,30].

The strengths of our study include its population-based design and recruitment from a well-defined and well-characterised healthy cohort. A small subsample of COVID-19 positive users with sufficient high-quality data (wearing the Ava-bracelet ≥ 28 days prior to SO), reliance on data from a single national centre, and lack of ethnic diversity may limit the generalisability of our findings. Additionally, we could not exclude imprecision or misclassification errors related to the symptoms experienced, dates of SO and/or SE. We acknowledge that our sensitivity was less than 80%. We expect to improve the algorithm`s performance further in a larger cohort within the setting of the COVID-RED study (n=20`000). Furthermore, our investigation was based on data from individuals younger than 51 years who typically show less severe symptoms. The algorithm could perform better in older people with more severe clinical

manifestations. This question will also be addressed within the framework of the COVID-RED study [13]. Finally, one could argue that about half of the individuals identified as positive by the bracelet did not show SARS-CoV-2 infection in subsequent laboratory testing, and an unnecessary testing burden could arise from this fact. The positivity rates of PCR testing (i.e. approximately 15%, depending on disease prevalence) [37,38] in symptomatic outpatients routinely tested during the pandemic which were considerably lower than the 50% observed in asymptomatic Ava-bracelet users. Hence, the Ava-bracelet could be regarded as progress when compared to the current testing routine.

Overall, the COVI-GAPP study showed that pre-symptomatic detection of COVID-19-related changes in physiological parameters using a sensor bracelet is feasible. We found significant changes in HR, HRV, and WST occurring in COVID-19 positive patients during the pre-symptomatic period compared to baseline measurements, over and above the effects of intrapersonal variability. A novel machine-learning algorithm detected 68% of laboratory-confirmed SARS-CoV-2 infections two days before SO. Wearable sensor technology is an easy-to-use, low-cost method for enabling individuals to track their health and well-being during a pandemic. Our research shows how these devices, partnered with artificial intelligence, can push the boundaries of personalised medicine and detect illnesses prior to SO, potentially reducing virus transmission in communities. Future research should focus on how medical-grade wearable sensor technology can aid in combatting the current pandemic by monitoring sensor data.

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Ethics approval and consent: The study was approved by the Ethics Committee of Zurich, Switzerland (BASEC 2020-00786; date of approval: April 9th, 2020). Informed consent was obtained from all study participants.

Data availability statement: Anonymized data that underlie the results reported in this article are available upon justified request to the corresponding author.

Competing interests: Lorenz Risch, and Martin Risch are key shareholders of the Dr Risch Medical Laboratory. David Conen has received consulting fees from Roche Diagnostics, outside of the current work. The other authors have no financial or personal conflicts of interest to declare.

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Table 1. Overall participant characteristics stratified according to whether they contracted COVID-19

Variables	Total n=1163	COVID-19 n=127	No COVID-19 n=1036	Test Statistic	Significance (*p* value)
Sex ratio (F:M)	667:494	74:53	594:441	$\chi^2(4)=0{\cdot}40$	0·982
Mean age, years (SD)	44·08 (5·57)	43·66 (5·64)	44·14 (5·56)	F(1, 1071)=0·59	0·444
BMI, kg/m² (SD)	24·72 (3·97)	24·74 (4·00)	24·72 (3·97)	F(1, 1071)=0·02	0·90
Smoking status, *N* (never: current: past smoker)	654:110:102	93:10:12	561:100:90	$\chi^2(2)=2{\cdot}38$	0·304
***N* of household contacts with COVID-19**	111	53	58	$\chi^2(1)=127{\cdot}94$	<0·0001*
***N* of work colleagues with COVID-19**	279	49	230	$\chi^2(3)=27{\cdot}3$	<0·0001*

* *indicates p≤ 0·002, significant difference with Bonferroni correction*

Table 2. Clinical characteristics of participants who contracted COVID-19 stratified according to whether they did (compliant group) or did not (non-compliant group) wear the bracelet regularly

Variables (n)	Compliant group (n=66)	Non-compliant group (n=61)	Test statistic	Significance (*p* value)
Sex ratio (F:M)	45:21	29:32	$\chi^2(1)=4{\cdot}74$	0·030
Mean age, years (SD)	42·88 (5·59)	44·54 (5·60)	F(1, 116)=2·85	0·094
BMI, kg/m² (SD)	23·75 (3·69)	25·81 (4·06)	F(1, 116)=10·39	0·002*
Hospitalization rate	3	7	$\chi^2(1)=0{\cdot}64$	0·425
Smoking status, *N* (never: current: past smoker)	57:4:5	36:6:7	$\chi^2(2)=3{\cdot}03$	0·22
N of household contacts with COVID-19	35	18	$\chi^2(1)=2{\cdot}39$	0·123
N of work colleagues with COVID-19	28	21	$\chi^2(1)=0$	1
COVID-19 symptoms:				
Fever	17	23	$\chi^2(1)=0{\cdot}89$	0·344
Chills	14	11	$\chi^2(1)=0{\cdot}62$	0·432
Cough	26	30	$\chi^2(1)=0{\cdot}25$	0·616
Runny nose	26	25	$\chi^2(1)=0{\cdot}01$	0·938
Difficulty breathing	11	10	$\chi^2(1)=0{\cdot}39$	0·530
Loss of the sense of smell	26	24	$\chi^2(1)=0{\cdot}37$	0·543
Loss of the sense of taste	20	22	$\chi^2(1)=0{\cdot}02$	0·896
Chest pressure	7	10	$\chi^2(1)=0{\cdot}22$	0·636
Sore throat	18	19	$\chi^2(1)=0{\cdot}00$	1
Muscle pain	27	32	$\chi^2(1)=0{\cdot}29$	0·593
Headache	44	29	$\chi^2(1)=7{\cdot}88$	0·005
Fatigue	27	38	$\chi^2(1)=2{\cdot}24$	0·135

Variables (n)	Compliant group (n=66)	Non-compliant group (n=61)	Test statistic	Significance (*p* value)
Malaise	19	25	$\chi^2(1)=0{\cdot}18$	0·670
Diarrhoea	13	13	$\chi^2(1)=0{\cdot}02$	0·896
Sickness	9	5	$\chi^2(1)=1{\cdot}29$	0·256
Vomiting	1	5	$\chi^2(1)=1{\cdot}89$	0·169
Hospitalization	3	7	$\chi^2(1)=0{\cdot}64$	0·425
Long-term effects of COVID-19 (≥10d)	5	15	$\chi^2(1)=5{\cdot}69$	0·017
Mean symptom duration	8·54 (5·10)	10·16 (10·98)	F(1, 116)=1·31	0·254

** indicates p≤ 0·002, significant difference with Bonferroni correction*

Table 3. Multi-level linear mixed models reveal the relationship between COVID-19 phases and physiological parameters

Predictors		Respiratory rate	Heart rate	Heart rate variability (SDNN[1])	Heart rate variability (RMSSD[2])	Heart rate variability ratio	Wrist skin temperature	Skin perfusion
Intercept		15·10† (0.26)	55·43† (0.83)	59·64† (1.43)	43·71† (1.16)	0·50† (0.02)	35·32† (0.06)	-0·01† (0·00)
COVID-19 phase								
	Baseline	**Reference group**	**Reference group**	**Reference group**	**Reference group**	**Reference group**	**Reference group**	**Reference group**
	Incubation	0·02 (0·06)	0·87† (0·29)	-1·48* (0·59)	-0·37 (0·48)	-0·01* (0·01)	0·13† (0·04)	0·00 (0·00)
	Pre-Symptomatic	0·14 (0·12)	1·00† (0·36)	-1·70* (0·64)	-0·75 (0·53)	-0·02* (0·01)	0·18† (0·05)	0·00 (0·00)
	Symptomatic	1·00† (0·18)	2·15† (0·48)	−1·45* (0·73)	0·12 (0·51)	0·00 (0·01)	0·30† (0·05)	0·00 (0·00)
	Recovery	0·10 (0·06)	0·87† (0·22)	-0·92 (0·51)	0·04 (0·44)	0·00 (0·01)	0·20† (0·03)	0·00 (0·00)

Unstandardized β -coefficient values reported, with standard errors in brackets.

*Note: *, † refer to p< 0·05, 0·007, respectively, with Bonferroni correction.*

[1]*SDNN: standard deviation of the NN interval.*

[2]*RMSSD: root mean square of successive difference.*

Table 4. Performance metrics of the algorithm in the detection of COVID-19 two days prior to symptom onset

Class 1 represented an 8-day long training instance extracted from day 10 to day 2 before SO. Class 0 represented a training instance extracted from all other 8 days long consecutive measurements (e.g., SO-11 to SO-3). The training set consisted of 40 days measurements from 66 participants with 70:30 train-test split. Sensitivity is reflected in the recall of class 1, while specificity is determined by the recall of class 0.

Sample	Class	Precision	Recall	F-Score
Training Set	0	0.60	0.45	0.51
	1	0.60	0.73	0.66
Test Set	0	0.50	0.36	0.42
	1	0.54	0.68	0.60

Figure Legends

Figure 1.

COVI-GAPP participants (n=1163) wore a certified medical device at night while they slept, syncing it to a complementary smartphone application upon waking. The device and app were originally designed for fertility tracking in naturally menstruating women but adapted for the purposes of this study. Instead of real-time fertility indications, participants saw “Fertility Unknown” upon syncing (A). Additionally, the in-app Daily Diary asked participants about potential confounds (B) and COVID-19 symptoms (C) rather than fertility-related questions.

Figure 2.

Recurrent Neural Network (RNN) architecture for the detection of a pre-symptomatic case of COVID-19. The RNN consisted of two hidden layers and one output layer. The first hidden layer contained 16 and second layer contained 64 long short-term memory (LSTM) units. The LSTM output activation was a sigmoid function, while the recurrent activation on hidden layers was the ReLU (Rectified Linear Unit) function. The input of RNN was 8 consecutive values of physiological signal originating from 8 consecutive nights of data. The output was an indication about the potential COVID-19 infection.

Figure 3.

Class depiction based on the recurrent neural network (RNN). Here, class 0 represents healthy days and class 1 represents the pre-symptomatic phase of COVID-19 (SO-10 to SO-2). Vectors of marked classes represent training input for the RNN.

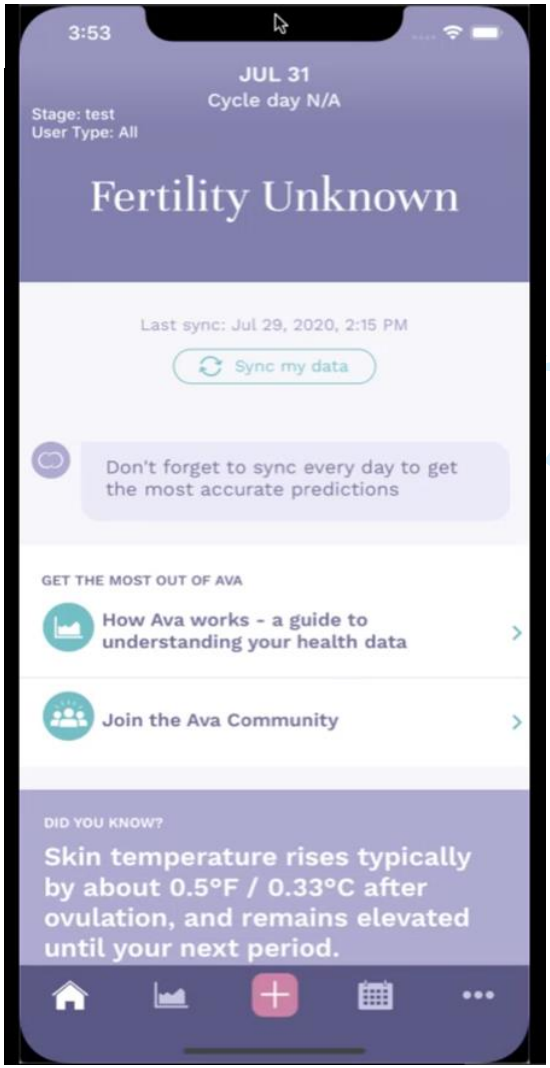
Figure 4.

Study flowchart. From 2170 GAPP participants, 1163 participants were enrolled in the COVI-GAPP study. 127 participants presented laboratory-confirmed COVID-19 disease and from these, a total of 66 positive tested participants had complete bracelet data available used for the algorithm development.

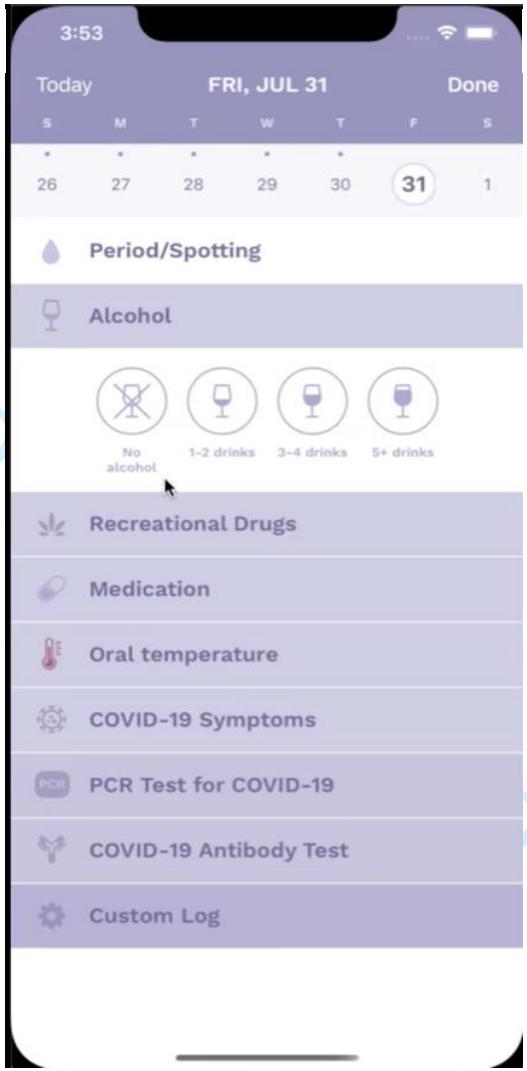
Figure 5.

The wearable device can detect changes in 5 physiological parameters across the clinical course of COVID-19. The values of each physiological parameter (with 95% CIs) collapsed across individuals (n=66) were normalized using baseline measurements and are shown centred around participant-reported symptom onset (SO).

A

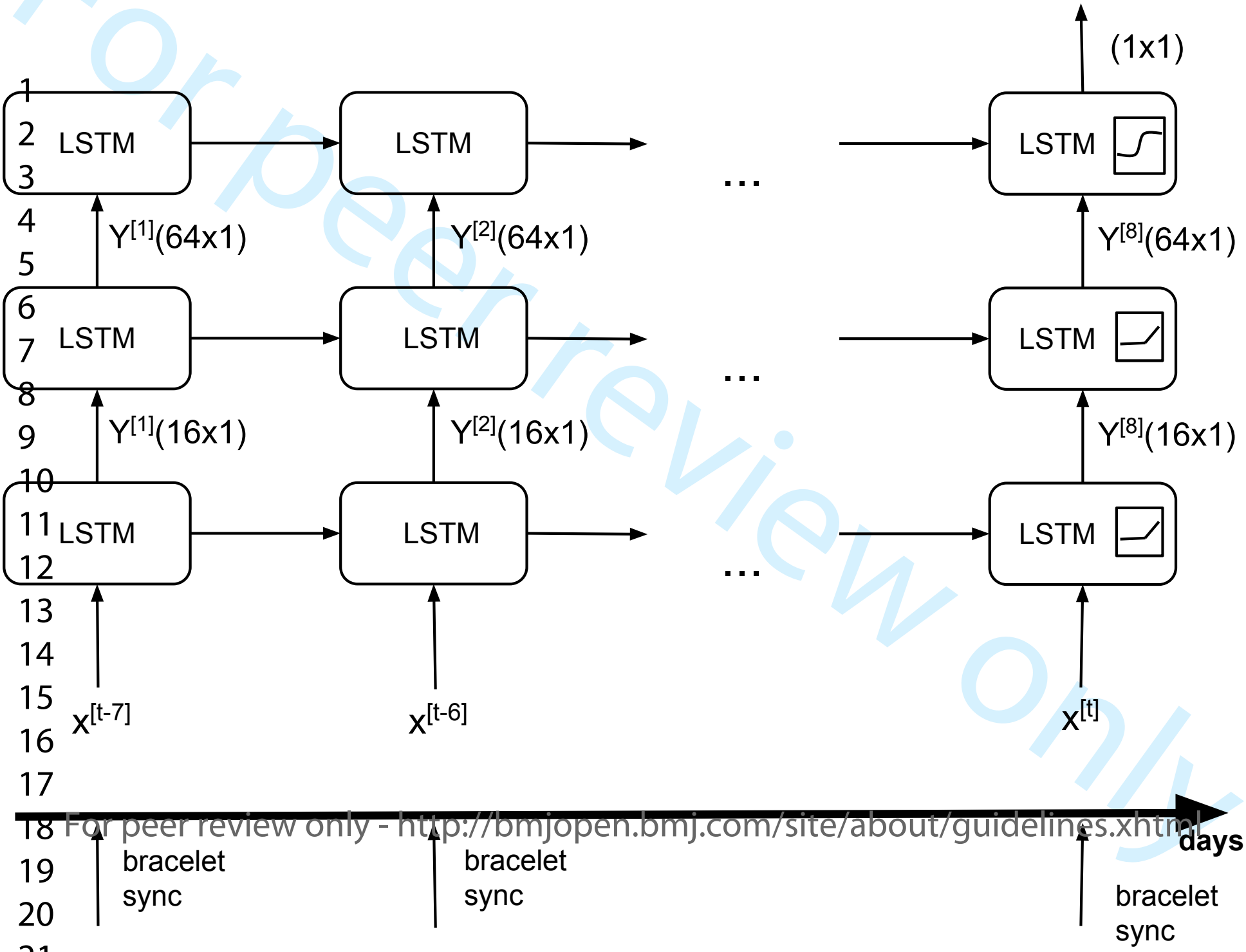

3:53
JUL 31
Cycle day N/A
Stage: test
User Type: All
Fertility Unknown
Last sync: Jul 29, 2020, 2:15 PM
Sync my data
Don't forget to sync every day to get the most accurate predictions
GET THE MOST OUT OF AVA
How Ava works - a guide to understanding your health data
Join the Ava Community
DID YOU KNOW?
Skin temperature rises typically by about 0.5°F / 0.33°C after ovulation, and remains elevated until your next period.

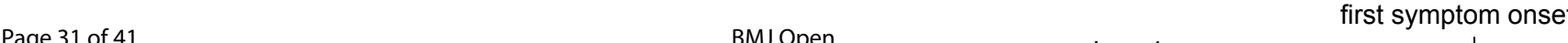
B

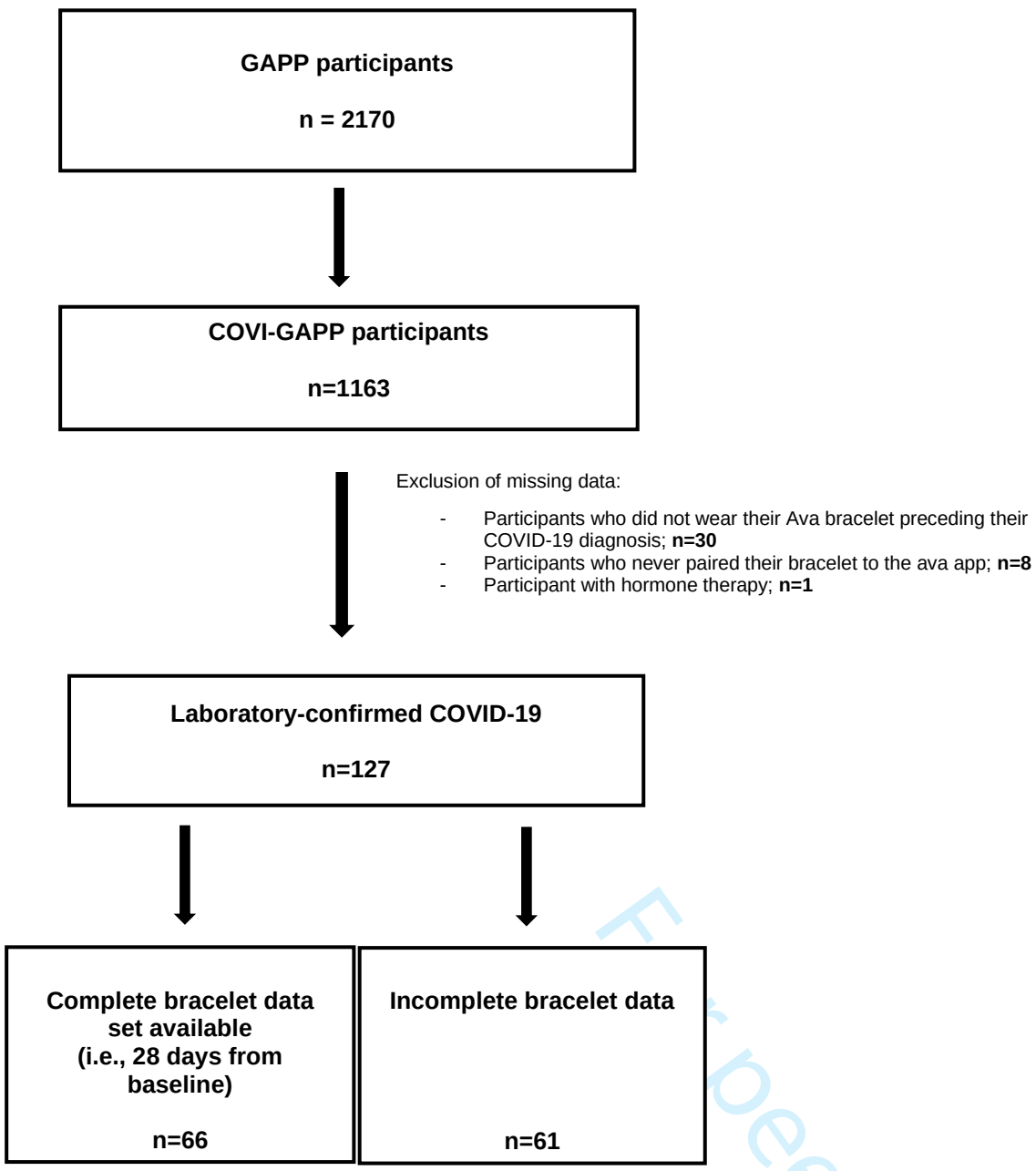

3:53
Today
FRI, JUL 31
Done
S M T W T F S
26 27 28 29 30 31 1
Period/Spotting
Alcohol
No alcohol
1-2 drinks
3-4 drinks
5+ drinks
Recreational Drugs
Medication
Oral temperature
COVID-19 Symptoms
PCR Test for COVID-19
COVID-19 Antibody Test
Custom Log

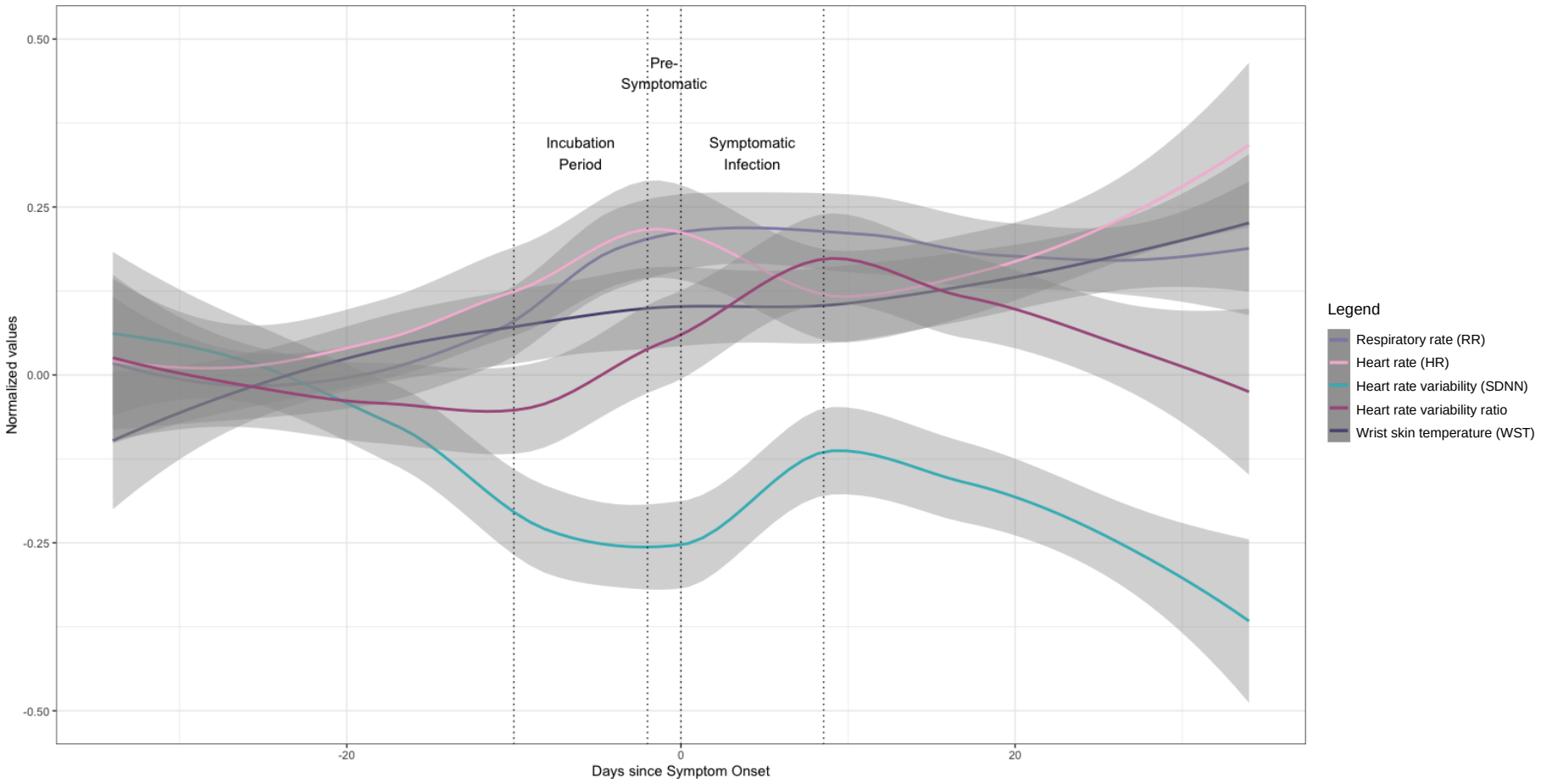
C


3:53
Today
FRI, JUL 31
Done
S M T W T F S
26 27 28 29 30 31 1
Medication
Oral temperature
COVID-19 Symptoms
Chills
Diarrhea
Dry cough
Fatigue
Fever
Loss of smell
Loss of taste
Muscle or body aches
Nasal congestion or runny nose
Shortness of breath or difficulty breathing
Sore throat
Vomiting








0.50
0.25
0.00
-0.25
-0.50
Normalized values
Pre-
Symptomatic
Incubation
Period
Symptomatic
Infection
-20
0
20
Days since Symptom Onset
Legend
Respiratory rate (RR)
Heart rate (HR)
Heart rate variability (SDNN)
Heart rate variability ratio
Wrist skin temperature (WST)

Supplementary Materials

Supplement to: "*Investigation of the use of a sensor bracelet for the pre-symptomatic detection of COVID-19: An interim analysis of a national cohort study (COVI-GAPP)*".

Supplementary Material and Methods

Our primary aim was to understand how the coronavirus disease 2019 (COVID-19) affects physiological parameters measured by a wearable device and, subsequently, whether these parameter changes could help in detecting a pre-symptomatic infection. In particular, we investigated how heart rate (HR), respiratory rate (RR), heart rate variability (HRV), wrist-skin temperature (WST), and skin perfusion deviated from baseline measurements during four infection-related periods: the incubation period, the pre-symptomatic period, symptomatic infection period, and the recovery period. We categorized daily parameter measurements as occurring in the baseline period if the day (d) was more than 10 days prior to symptom onset (SO; i.e., d>SO-10). Relatedly, we defined the incubation period as SO-10≤d<SO-2 and the pre-symptomatic period as SO-2≤d<SO. Because participants' reported symptom duration varied, measurements fell into the symptomatic infection category if SO≤d≤SE. Finally, parameters collected after symptom end (SE) were classified as in the recovery period (i.e., d>SE).

The Wearable Device and Physiological Parameter Specification

The Ava Fertility Tracker (version 2·0; Ava AG, Switzerland) is an United States Food and Drug Administration (FDA) cleared and conformité européenne (CE) certified fertility aid bracelet that complies with international regulatory requirements and applicable standards.[1,2] The wrist-worn tracker consists of three sensors: a temperature sensor; an accelerometer; and a photoplethysmograph (PPG).[3] The Ava-bracelet saves data every 10 seconds and requires at least four hours of relatively uninterrupted sleep to record enough data for pre-processing and analysis. Upon waking, the user taps a button in the complementary smartphone app to initiate the previous night's raw data transfer from the Ava-bracelet to the system's backend database via Bluetooth Low Energy (BLE). The data then undergoes pre-processing according to proprietary manufacturer algorithms to remove potential artifacts, detect the user's sleep stages, and identify nightly physiological parameters. In addition to the algorithm-derived fertility indication, the post-processing values for HR, WST, RR, sleep quantity, sleep quality, and HRV ratio are then sent back to the complementary app and displayed to the user. The device's sensors responsible for recording the raw data are described in detail below as well as show in Figure S1.

Built into the Ava-bracelet's internal hardware, the accelerometer detects and records the wearer's movement in three-dimensional space. A proprietary machine learning algorithm ingests nightly movement data to determine sleep stages. In addition to reporting the user's duration of sleep in-app, it also assigns her a nightly sleep quality score consisting of the percentage of combined deep and Rapid Eye Movement (REM) sleep. Although other researchers have examined COVID-19's impact on sleep using wearable devices with mixed or inconclusive results[4–7], since sleep quality and quantity were not among our pre-defined primary objectives we did not analyse results from the accelerometer data.

A temperature sensor constitutes the Ava-bracelet second sensor and provided data for evaluating COVID-19 related changes in wrist skin temperature (WST). Despite the device reading temperature at a distal point compared to core body temperature, recent research has demonstrated the Ava-bracelet's ability to continuously measure temperature throughout the night results in more sensitive readings than oral point estimates and enables its machine learning algorithms to detect more ovulation-related changes in temperature.[8] These findings suggest the medical grade device's ability to sense fluctuations in WST related to an infection would similarly benefit from its repeated sampling over the course of sleep and may outperform an oral or forehead reading taken only once at point of care (POC). Limited evidence conducted early on during the COVID-19 pandemic attests to WST's potential superior usage in detecting infection-based fluctuations; WST for 528 patients read by a noncontact infrared thermometer proved more stable and less prone to environmental factors (e.g., walking or bicycling to POC) than tympanic and forehead measurements in some contexts. Thus, given prior research on the Ava-bracelet's measurement accuracy compared to oral temperature and on WST's importance in triaging COVID-19 patients, we relied on the device's temperature sensor to provide nightly WST readings for analysing how temperature changes across a symptomatic SARS-CoV-2 infection.

A PPG comprises the Ava bracelet's final sensor. The PPG sensor employs a light emitting diode (LED) current to send infrared light through the user's skin to detect inter-beat intervals (IBIs). The light reflects off or is absorbed by the blood; how much light bounces back to the sensor can signal the wearer's current cardiac rhythms.[9] Based on the time cadence for variance in the reflected light, proprietary algorithms can determine the user's HR, RR,

perfusion and IBI; in turn, the IBI can inform calculations for various metrics of HRV. While HR consists of the number of heart beats per minute, HRV describes the fluctuation in time intervals between consecutive heartbeats.[10] It can vary in both frequency- and time-domains, resulting in more than 20 possible metrics for quantifying the heart's activity.[10] Since examining all HRV metrics would have proven practically and statistically infeasible, we focused on two time- and one frequency-domain measurements. The first time-domain measure of HRV, the standard deviation of the NN interval (SDNN), quantifies sympathetic and parasympathetic nervous system activity in ms; it describes how much variability exists in the interval between normal sinus beats.[10] A lower SDNN corresponds to impaired cardiac health[10], with recent research offering conflicting evidence about SDNN's changes in COVID-19 patients. While some studies demonstrated an increase in SDNN among COVID-19 patients[11], others have found changes in SDNN dependent upon disease severity.[12] Regardless of the effect's direction, we expected an individual suffering from COVID-19 would exhibit deviations from their baseline SDNN during an active infection and included it in our analyses. A second time-domain measurement of HRV, the root mean square of successive differences (RMSSD), examines the variability between normal heartbeats. Increased RMSSD has previously been shown to be associated with severe infection, including septic shock and COVID-19.[11,13] Thus, we focused on RMSSD changes across the incubation, pre-symptomatic, symptomatic and recovery phases compared to participants' baseline measurements in our analysis. The final HRV parameter we examined, the HRV ratio, constitutes a frequency-domain measurement; it indicates the ratio of HR oscillations in the low-frequency (LF; 0·04-0·15 Hertz [Hz]) to those in the high-frequency (HF; 0·15-0·4 Hz) bands[10,14]. Patients with severe COVID-19 infection have exhibited a higher HRV ratio than mildly infected participants[12], leading us to examine this physiological parameter in our analyses.

Data Processing and Multi-level Model Specification

We performed all data processing and analysis using R (R Core Team, v3·6·1[15]) and Python (Python Software Foundation, v3·6[16]). In keeping with data cleaning practices described by the manufacturer in previous publications,[3] we excluded the first 90 and the last 30 minutes of data from each night a priori from our analysis; transitions from waking to sleeping and vice versa can result in greater variation in physiological parameters measured by the Ava-bracelet, thereby leading to less stable readings. To further reduce artificial fluctuations in the data due to potential measurement error and consistent with best practices[17], each physiological parameter underwent locally estimated scatterplot smoothing (LOESS) prior to analysis.

Next, we ran a series of multi-level models with random intercepts and random slopes to determine differences in physiological parameters during the infection-related periods compared to baseline, accounting for the nesting of repeated measurements during an infection period and within an individual. Given our continuous criterion, we used the "lme" function with residual maximum likelihood estimation (REML) and Satterthwaite degrees of freedom in the open-source R packages "lme4"[18], "lmerTest"[19], and "optimx"[20] to model our outcomes of interest. Four dummy-coded variables were created, indicating to which infection period a given measurement belonged (1= Belonging to that Period, 0=Not belonging to that period). The reference baseline period measurements were encoded as 0 across all four dummy variables. Our reported results include the unstandardized regression coefficients for each effect. When multiple models were possible for the same parameter, we chose the model using the percentile of data (stable maxima) with the best fit; we determined best fit by comparing the two models using an analysis of variance (ANOVA) test and selecting the model with the significantly lower Akaike Information Criterion (AIC). In instances where the models were not significantly different from each other, we chose the model that included more data (e.g., the 99% percentile of data versus the 90th percentile).

In an effort to provide some context for the magnitude of our significant effects, we report the intraclass correlation coefficient (ICC) for each of the null models associated with changes in physiological parameters over the course of a COVID-19 infection. The ICC indicates how much variance in an outcome occurs due to between group differences[21–23]; in the context of the current study, the ICC presents a picture of how a given physiological parameter varies due to participant-level characteristics versus the within-subject course of a COVID-19 infection.

To ensure a family-wise alpha level less than or equal to ·05, we implemented a Bonferroni correction for the seven total parameters we analyzed and evaluated effect significance using this new level of p=·007. We adjusted how we defined marginal significance accordingly (i.e., ·007≤p≤·05). We used the Bonferroni-corrected significance level throughout the paper.

Supplementary Results

The ICCs and random effects variance estimates for each of the seven multi-level models can be found in Table S1. In brief, most physiological parameters had high levels of variance which could be attributed to between participant differences rather than within subject changes due to COVID-19 infection.

For most physiological parameters, observed variance in the outcome resulted largely from a participant's own stability in readings over time. All cardiac parameters showed similar ICCs, ranging from 0·71 (RMSSD) to 0·77 (SDNN); this means that, depending on the parameter, 71-77% of the variance in outcome was due to between participant differences. Regardless of infection phase, a given participant's nightly cardiac measurements were more similar to one another than random chance. RR showed an even higher ICC; 88% of all observed variance in RR was attributable to between participant differences. A maximum of 22% of variance could be due to within participant changes. The multi-level model testing the effect of infection phase on nightly RR reveals only a significant difference between the symptomatic period and baseline (see Table 3); all other phases do not differ significantly from baseline, illustrating the lack of overall variability due to a COVID-19 infection and emphasizing RR's stability over time within an individual participant.

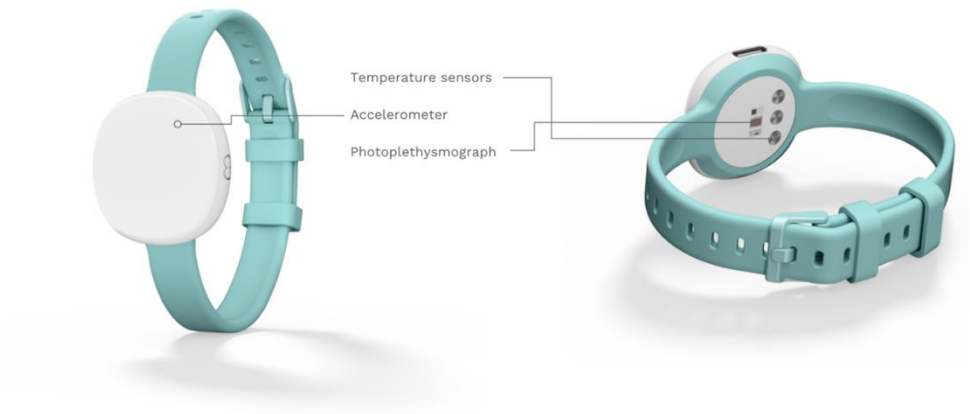
On the other end of the spectrum, only wrist skin temperature and perfusion had low ICC's (0·01 and 0·05, respectively); said differently, a given participant's perfusion or temperature measurements over time were not more similar to each other than would be expected from a random selection of that same parameter across all participants. As perfusion did not show phase-based changes in COVID-19 infection (see Table 3), it may be that another unaccounted for factor contributes to outcome measurements. Neither the participant's own repeated measurements nor the disease trajectory appear to significantly influence a given night's perfusion data. In contrast, since wrist skin temperature significantly differed from baseline across all other phases of a COVID-19 infection (see Table 3), it appears that the disease itself contributes more to a given night's temperature readings than the stability in a participant's own repeated measurements; almost all of the observed variance in nightly skin temperature occurs due to within participant differences (e.g., changes in their physiology over the course of the infection). Examining ICC values for each physiological parameter of interest provides greater context into the relative effect of potential phase-based changes in outcome variables as well as the residual variance attributable to the participant themselves.

Supplementary Tables and Figures

Supplementary Table 1. Intraclass correlation coefficients (ICCs) calculated based on the variance estimates for random effects of the null models predicting each of the seven physiological parameters of interest**.**

Predictors	Between Participant Variance (SD)	Variance of the Residuals (SD)	ICC
Wrist Skin Temperature	0·34 (0·59)	35·65 (5·97)	0·01
Heart Rate	43·59 (6·60)	13·53 (3·68)	0·76
Heart Rate Variability (SDNN)	121·64 (11·03)	36·08 (6·08)	0·77
Heart Rate Variability (RMSSD)	82·08 (9·06)	33·79 (5·81)	0·71
Heart Rate Variability Ratio	1·16 (1·08)	0·40 (0·63)	0·74
Respiratory Rate	4·48 (2·12)	0·64 (0·80)	0·88
Skin perfusion	3·8 e-05 (0·01)	6·75 e-04 (0·03)	0·05

Supplementary Figure 1. The Ava Fertility Tracker contains three sensors (temperature, accelerometer and photoplethysmograph) that measure wrist skin temperature, heart rate, respiratory rate, heart rate variability and skin perfusion simultaneously.



Study protocol

The study protocol can be downloaded here.

Supplementary references

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-13
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	21-25
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	21-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5-9
	9	Whether participants formed a consecutive, random or convenience series	5-9
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6
	11	Rationale for choosing the reference standard (if alternatives exist)	NA
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	NA
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	NA
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	NA
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	NA
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	6
	15	How indeterminate index test or reference standard results were handled	6
	16	How missing data on the index test and reference standard were handled	NA
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	NA
	18	Intended sample size and how it was determined	5-9
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 4
	20	Baseline demographic and clinical characteristics of participants	10-12
	21a	Distribution of severity of disease in those with the target condition	10
	21b	Distribution of alternative diagnoses in those without the target condition	10
	22	Time interval and any clinical interventions between index test and reference standard	10
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	NA
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	10-12
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	15
	27	Implications for practice, including the intended use and clinical role of the index test	14-15
OTHER INFORMATION			
	28	Registration number and name of registry	5
	29	Where the full study protocol can be accessed	5
	30	Sources of funding and other support; role of funders	17

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.